Children with severe acute malnutrition
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Chapter 7

Summary, General Discussion and Conclusions

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SUMMARY AND GENERAL DISCUSSION

Forty-five percent of worldwide deaths in children under-5 years of age is directly or indirectly attributable to poor nutrition.(1,2) Tackling the global problem of malnutrition and of severe acute malnutrition (SAM) in particular, to increase health, quality of life, and to reduce under-5 mortality, is now receiving much greater attention from the international community. This is demonstrated, among others, by its inclusion in the United Nations’ Sustainable Development Goals.(2)

The aim of this thesis is to gain further insight into how to improve diagnosis and treatment of children with complicated SAM. In this thesis we described the results of two randomized controlled intervention trials, two observational studies and one systematic review.

Severe Acute Malnutrition and the exocrine pancreas

In the first three chapters we explored the relationship between exocrine pancreatic insufficiency (EPI) and SAM, and the prevalence and treatment of EPI in children with complicated SAM.(3–5) EPI results in impaired digestion because of the central role of the exocrine pancreas in nutrient digestion. EPI can cause diarrhea; one of the common complications in children with SAM, which can greatly increase mortality.(6–8) EPI can be treated by supplying the pancreatic enzymes through pancreatic enzyme replacement therapy (PERT).(9,10) The relationship between EPI in malnutrition in children had been described previously, but it was unclear if malnutrition led to EPI, or vice versa. Previous studies, mostly performed between 1940 and 1980, found that children with SAM also have EPI.(11–22) While it was also known that children with EPI as a complication of an underlying illness, are at risk of becoming malnourished.(23–25)

To find out whether malnutrition led to EPI, or vice versa, we systematically assessed the evidence concerning the relation between EPI and malnutrition in children, as presented in chapter 2. We performed database searches to find studies reporting on prevalence or incidence of EPI and malnutrition in children. Nineteen studies were included and divided into two groups: ten studies reporting on patients diagnosed with EPI who were later found to be malnourished, all conducted in cohorts of patients with an underlying disease leading to EPI (i.e. Cystic Fibrosis (CF), Chronic Pancreatitis, Human Immuno-deficiency Virus (HIV), Shwachmann-Diamond Syndrome (SDS) and celiac disease), and nine studies reporting on patients diagnosed with malnutrition who were later found to have EPI. This last group mostly performed in a low resource setting. Studies included were published between 1952 and 2016, and showed large heterogeneity in: quality (i.e. mainly small sample sizes), design, definitions used and outcome measures (using techniques that are not up to current gold standard). This heterogeneity inhibited us to conduct a quantitative analysis, and limited us in drawing firm conclusions. Although EPI
was linked to decreased nutritional status, this link was not specified properly in most articles. We concluded that there is sufficient evidence for an association between EPI and malnutrition, but could not confirm whether there is a causal relationship between the two. More longitudinal clinical trials, using standardized definitions and (current) gold standard techniques are needed to explore this relationship further. A problem however, in exploring this relation in future research, is that a placebo arm (withholding treatment of EPI in children with underlying diseases) would not be ethical, because treatment for this group is part of standard clinical practice. Because children with SAM (and EPI) are very vulnerable patients, we decided to focus on SAM patients with EPI and explore whether treatment of EPI could improve their clinical outcome.

Before we could start this investigation, it was necessary to determine the prevalence of EPI amongst children with complicated SAM. Therefore, we studied the pancreatic function in Malawian children with complicated SAM, as described in chapter 3. We recruited 89 children admitted to Queen Elizabeth Central Hospital in Blantyre, Malawi with complicated SAM, and tested their pancreas function, using the sensitive and specific EPI-marker Fecal Elastase-1 (FE-1). In addition to this, we measured their serum trypsinogen and amylase levels, which are released by damaged pancreatic cells, and are used as markers of pancreas inflammation.\(^ {26,27}\) We found that 92.2\% of patients showed evidence of EPI on admission, and 76.6\% showed evidence of severe EPI. Prevalence of EPI was significantly higher and more severe in children with edematous SAM compared with those with non-edematous SAM. Though we found some improvement of the pancreas function during admission, with increasing FE-1 levels, these values did not normalize. Also, we found elevated levels of trypsinogen and amylase, suggesting pancreatic inflammation. Mortality in the entire study cohort was 15.7\%, with a significantly higher number of children dying with non-edematous SAM than edematous SAM. However, no differences in mortality were found between pancreatic sufficient versus insufficient patient groups.

We concluded that EPI is highly prevalent in children with SAM, especially in children with edematous SAM, and that biochemical signs suggestive of pancreatitis are common in children with SAM.

We cannot clarify but only speculate about the interesting difference in the prevalence of EPI between the two phenotypes in malnutrition (edematous vs. non-edematous). One of the potential explanations could be that edematous malnutrition or kwashiorkor is a different entity than non-edematous malnutrition or marasmus. The fact that WHO advises to treat the two phenotypes with one blanket approach might at some point change when more evidence is found that the two phenotypes are indeed also pathophysiologically different than is currently thought. In the 1980’s post-mortem analyses showed differences in liver pathology between the two phenotypical groups.\(^ {22}\) It would be of great interest to repeat these post-mortem studies, using modern techniques investigating pancreatic
architecture, organelle function, and inflammation makers. This might improve our understanding of the differences found in chapter 3 and hopefully lead to new, phenotype-tailored treatment options. The reason why we did not find differences in clinical outcomes in our cohort was likely due the small number of children without EPI in our cohort (n=6). It would be interesting to assess these differences in clinical outcome in malnourished children with and without EPI, both in the short and in the long-term, and to compare them with a control group by collecting data from healthy Malawian children. This could provide more in-depth insight in the underlying pathophysiology and the ‘pathways’ in which the exocrine pancreas is related to outcome.

As a next step we wanted to explore the possible benefits of PERT in children with complicated SAM. In chapter 4, we presented our findings of a randomized controlled trial in 90 children with complicated SAM. All children received standard care as per WHO and Malawian guidelines, while the intervention group also received PERT for 28 days. The primary outcome was weight gain (%), while secondary outcomes were pancreatic function (assessed by measuring FE-1), duration of hospital stay, mortality, and digestive function reflected by fecal fatty acid split-ratios. This ratio can reflect failed fatty acid breakdown (i.e., a high proportion of triglycerides in total fecal fatty acids) and/or failed absorption (i.e., a high proportion of free fatty acids in total fecal fatty acids).

Children treated with PERT did not gain more weight than controls. Similar to our findings in chapter 3, we found a high prevalence of EPI (83%) and severe EPI (69%) on admission. During the 28 days of the intervention, there was an improvement but no normalization of the pancreas function, irrespective of the treatment group. Again, children with edematous SAM showed more severe EPI and showed less improvement of FE-1 levels over time than children with non-edematous SAM. After 28 days of nutritional rehabilitation, irrespective of PERT, 68% of the study patients still showed EPI, and 46% still showed severe EPI. Duration of hospital stay was not found to be different between the groups. However, competitive risk analysis showed that, compared with controls, children receiving PERT had a significantly higher probability of being discharged on every passing day of treatment. An additional intriguing finding was that mortality overall was 27.8%, and was significantly lower in the intervention group. Eight children (18.6%) in the PERT group died versus seventeen (37.8%) in the control group. Finally, we found significantly lower fecal fatty acid split-ratios at admission in children that died compared to those that survived. This implies that a marker of poor fat digestion is associated with mortality.

We concluded that PERT does not improve weight gain in children with complicated SAM, but does increase their rate of hospital discharge and is associated with lower mortality. These chapters together provided new and thorough insight into the role of the pancreas in children with complicated SAM. We showed that despite treating EPI with PERT, our patients did not show improved weight gain. One of the explanations that an effect in weight gain is seen in children that are treated in the West with, for example, CF, is that...
these children tend to be in a much better nutritional status than the SAM children in our study. Also, the known malabsorption of the malnourished gut may inhibit optimal effect of the treatment. Giving PERT on its own to improve digestion does not have any beneficial effect when the next step, absorption, is dysfunctional as well. Several limitations need mentioning, such as the possibility of a too short duration of treatment and follow-up. We cannot rule out that treating longer than 28 days might result in improved weight gain. As a trend of improvement of pancreas function has been found in both chapter 2 and 3, it is of great interest to follow these patients over a longer time. With more intense follow-up we could observe if pancreas function eventually also normalizes with nutritional rehabilitation only, or whether this improvement stagnates after some time. If pancreas function normalizes just by nutritional rehabilitation alone, this would lead to the recommendation of not treating this specific patient group with PERT. Another limitation may have been weight gain as a primary outcome. Although a clinically important variable, it is both a noninvasive measuring tool and relevant for measuring nutritional status and improvement, it is also a less relevant variable in the sense that it may not represent the clinical status of a child in the acute setting, but has more value over longer periods of time. In the acute setting, the weight of children with SAM tends to fluctuate, and although these children improve clinically, they do not necessarily gain weight in those first days of nutritional rehabilitation. Also, there is an important difference in the course of weight gain throughout clinical stabilization and nutritional rehabilitation, between children with non-edematous and edematous SAM. Children with non-edematous SAM will normally show a slow increase of weight over time. In children with edematous SAM however, there is much more variation throughout admission. These children first lose their edema, and thus weight, before gaining weight. We corrected for this in our study by using their lowest weight throughout admission as their baseline weight. However, in some children their lowest weight was only reached a few days before discharge. So, for these edematous children, their weight gain was measured over a very short time period. Weight gain could be a good outcome in children with non-edematous SAM, but may not be ideal for those with edema.

We found significant differences in mortality amongst the groups, but had not powered the study for this variable. However, this secondary outcome is literally of vital importance, as the findings were significant and request further exploration. Before we can recommend that PERT has no importance in the treatment of children with complicated SAM, the influence of PERT on the mortality rate and discharge rate deserve to be studied in more detail. This study had not stratified for edematous status, and a higher portion of children with edematous SAM were found to be in the PERT intervention group. Recent studies have shown inconsistent findings of which phenotype of SAM is associated with higher mortality risk.(31,5,32) Even after correcting for edematous status, significant difference in mortality remained, so this cannot (fully) explain the lower mortality rate in
the PERT intervention group. The number of days until death were similar in both groups, around 4-5 days into admission. As such, the following questions need answers: Why would a SAM child treated with PERT have an improved survival risk? Does treatment with pancreatic enzymes improve their clinical recovery, and somehow protect some children with SAM from dying? Should we focus on subgroups to find these benefits? Would children with edematous SAM who have a higher prevalence and more severe degree of EPI, benefit from this treatment more than those without edema? There is a need for additional investigating into the potential benefits of PERT in a larger cohort, with stratification for edematous and non-edematous malnutrition, and with mortality as primary outcome. Future research should also focus on clarifying the exact ‘damage’ to the exocrine pancreas, or on more tailored diets that specifically address the impaired digestive function in SAM children. This could be done through post-mortem sampling of the pancreas, and by using diets used in pancreatitis; a state of increased inflammation of the pancreas.

Severe Acute Malnutrition and gut inflammation

In chapter 5 we focused on gut enteropathy in children with complicated SAM. Children with SAM have gut inflammation as a feature of intestinal pathology.(31) This inflammation has similarities to that which occurs in non-IgE mediated food allergy and Crohn’s disease, which are treated with elemental and polymeric feeds respectively.(33–35) As such, it may be possible that these feeds could also benefit children with SAM. To investigate this, we designed a randomized, controlled, three-arm intervention trial, recruited 95 children with complicated SAM, who were allocated randomly to receive, for two weeks, either standard dietary management with ready-to-use therapeutic food (RUTF), an elemental feed, or a polymeric feed. Primary outcome was fecal calprotectin, a non-specific biomarker of intestinal inflammation. Some of the secondary outcomes were other biomarkers of intestinal inflammation, mucosal integrity, systemic inflammation, and tolerability of feeds. In all children, we found highly abnormal levels of fecal calprotectin and other biomarkers at baseline, and these generally persisted in all three treatment arms. In addition, no clinical benefits were found in the two intervention groups, while the novel feeds were actually poorly tolerated by the children with SAM. In short, we concluded that both elemental and polymeric feeds did not have the anticipated anti-inflammatory or clinical benefits.

The most important limitations of this study were the duration of administration of the novel feeds and the smaller number of patients recruited than was the target (95 instead of 120). As for the duration of administration: although a longer period of feeding (4-8 weeks) is recommended to achieve clinical remission and mucosal healing, this was not feasible in our setting.(36,37) WHO and Malawian malnutrition guidelines recommend discharge once children are improving and tolerating RUTF, and on average this is before two weeks
of admission.\(28,29,38\) Requesting for patients and their guardians to stay in hospital for several additional weeks would result in lower consent rates, and would put them at higher risk of hospital-acquired infections, and therefore should be considered unethical. A solution could be to treat them as outpatients, but this would require intensive follow-up to make sure children are compliant to their diets, which is challenging in any setting, but even more so in a low resource setting with limited logistics and infrastructure. As for the recruitment below target: this was mainly caused by the lower number of admissions than in previous years. We managed to recruit 55% of eligible patients. The primary reason guardians gave for not giving consent was the prolonged hospital duration.

With this study we again demonstrated the complexity of the pathophysiology in children with complicated SAM, which has recently been described and summarized by Bhutta et al.\(31\) Clearly, in children with complicated SAM, the treatment of intestinal pathology is more complex than in populations with enteropathies alone, such as in non-IgE mediated food allergy and Crohn’s disease, in which used treatment feeds have a demonstrated beneficiary effect. This is similar to our findings in chapter 4, when PERT did not have the anticipated beneficial effect that is found when administered to children suffering from EPI secondary to an underlying illness that is more straightforward. The persistent inflammation of the malnourished gut despite receiving nutritional rehabilitation needs further exploration. It is important to know whether the cause of inflammation persists throughout nutritional rehabilitation, or whether it is due to hospital acquired infections. A confounder could be HIV enteropathy, which has also been previously described in children with SAM.\(39\) However, we found no differences when analyzing children with and without HIV separately.

Another important finding from our study is the lack of improvement in intestinal pathology, following current recommended WHO treatment for children with complicated SAM. A consequence of gut enteropathy is malabsorption, which means WHO recommended supply with RUTF does not currently have its optimal effect. To fill the current knowledge gap on pathophysiology should be a priority in order to better remedy enteropathy in children with SAM and optimize recovery.

Severe Acute Malnutrition and Bio-electrical Impedance Analysis

Finally, we were interested in finding new measurement tools for children with complicated SAM that would have a better prognostic value than classic anthropometry alone. It would be of interest to find new, noninvasive, and low-cost strategies that help in better predicting the severity and outcome of the illness of a child with complicated SAM. Bioelectrical impedance analysis (BIA) is an economical, noninvasive, safe, and easy to use technique for the assessment of body composition.\(40\) The technology determines the electrical impedance of body tissues, which provides an estimate of total body water as well as estimates of fat-free mass and body fat.\(40\)
Several studies had looked at BIA in children with SAM, but no longitudinal data were available yet.\(^{(41,42)}\) We developed a prospective study to explore the change of BIA throughout clinical stabilization in children with complicated SAM, and to investigate whether BIA would have added prognostic value to clinical outcome, compared to using classic anthropometry alone, which is reported in chapter 6. We studied 183 children with complicated SAM admitted to the ‘Moyo’ NRU, 11 healthy Malawian children, and measured their bio-electrical impedance parameters on admission and after clinical stabilization. We found that children with edematous SAM had significantly lower bio-electrical impedance parameters than non-edematous children and control subjects, and that only in the edematous group a significant change of BIA was measured over time, which reflects fluid loss. BIA parameters were not significantly associated with mortality, and had no added predictive value over classic anthropometry alone. With our PLS-DA models we showed that BIA helps marginally in separating the different nutritional groups. This means that the additional value of BIA may only be of significance when there is clinical doubt whether the (malnourished) child has edema.

We concluded that throughout clinical stabilization, BIA showed changes in children with edematous SAM, but that BIA did not provide any significant contribution to predict clinical outcome than classic anthropometry. This study did not clearly identify a role for the clinical use of BIA for children with complicated SAM.

We analyzed our data in multiple ways in order to be able to give firm advice on whether or not BIA in children with SAM should have a role or deserves further exploration. We did not look at long-term follow up and BIA in relation to clinical outcome later in time. For example, it could still be of interest to find out how body composition of children recovered from complicated SAM adjusts. Do they gain fat mass or lean mass? These questions may deserve further exploring in future research. However, we know that in a NRU with low resource setting, BIA is of no added value and does not need further exploration.
CONCLUSIONS AND RECOMMENDATIONS

In conclusion, in children with complicated SAM we found

- an extremely high prevalence of EPI, but treatment with PERT for 28 days did not improve EPI or clinical status of the child with SAM. Nutritional rehabilitation on itself did significantly improve the EPI, however, pancreatic function had not normalized after 28 days

- enteropathy, but treatment with elemental and polymeric feeds did not significantly improve the enteropathy, and neither did it contribute to faster clinical recovery of the child with SAM

- that bio-electrical impedance analysis does not add any prognostic or clinical value to classic anthropometry, and hence does not seem a useful tool in this specific patient population.

This thesis has increased our insight into potential new diagnostics and treatment strategies in children with complicated SAM. Intervention studies in low resource settings, and in children with complicated SAM in particular, are extremely challenging, which likely explains the few existing publications despite the scale of the problem. Therefore, this thesis makes a significant contribution to the limited published research: apart from the main conclusions on the different specific topics, it has underlined the complexity of this disease, the large deficit in current knowledge and management, and the urgent need for more research to better understand the pathophysiology of this disease in order to stimulate development of interventions that address the unacceptably high case-fatality and poor long-term outcomes of children with complicated SAM. Despite the logistical difficulties and challenges in performing high quality research inherent to studies on this subject, it is of vital importance that we prioritize this research with funds and other resources - for the difficulties in finding scientific significance are trumped a thousand-fold by the ethical relevance of the suggested research: our children depend on us to tackle this problem now, so that they may live a healthy life. In Malawi, two examples of great projects focusing on the problem of childhood malnutrition are CHAIN (‘CHildhood Acute Illness and Nutrition Network’ http://www.chainnetwork.org/) and Project Peanut Butter (http://www.projectpeanutbutter.org/). CHAIN was started recently, and is funded by the Bill & Melinda Gates Foundation. It is a global research network focusing on “optimizing the management and care of highly vulnerable children in resource-limited settings to improve survival, growth and development”. Moyo NRU is included in this network as one of their many research sites. Project Peanut Butter has its focus on community management of malnutrition in several African countries and “seeks to advance the treatment of severe malnutrition, the single largest cause of child death in the world today, using effective, locally produced ready-to-use therapeutic foods”. They are responsible
for the first factory in Malawi to produce RUTF with local product, and which is run by local staff. It is projects like these that need our ongoing (financial) support, as they make a substantial difference for the malnourished child and their community.

With more funds and more researchers to perform more observational and interventional research, we will be able to succeed in tackling this global burden of childhood malnutrition, and to contribute to the nutritionally healthy future of children recovering from SAM and of those yet to be born.

Our children’s futures are not to be wasted.
REFERENCES


