REFEEDING SYNDROME CHARACTERISED BY HYPOPHOSPHATAEMIA IN CHILDREN 0 – 59 MONTHS DIAGNOSED WITH SEVERE ACUTE MALNUTRITION IN A SOUTH AFRICAN SETTING

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DECLARATION

"I, Natalie Fourie, declare that the Master's Degree research dissertation or interrelated, publishable manuscripts/published articles, or coursework Master's Degree mini-dissertation that I herewith submit for the Master's degree in Dietetics, at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education."

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LIST OF ABBREVIATIONS

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SAM:	Severe acute malnutrition	1
SD:	Standard deviation	1
MUAC:	Mid-upper arm circumference	1
RFS:	Refeeding syndrome	1
HIV:	Human immunodeficiency virus	1
INR:	International normalised ration	1
UTI:	Urinary tract infection	1
TB:	Tuberculosis	3
CRP:	C-reactive protein	4
NCR:	Nutrition Care Record	8
UNICEF:	The United Nations Children's Fund	17
PEM:	Protein-energy malnutrition	20
NICE:	National Collaborating Centre for Acute Care	33
RCPCH:	Royal College of Paediatrics and Child Health	59
ALT:	Alanine aminotransferase	61
TBIL:	Total bilirubin	61
ALP:	Alkaline phosphatase	61
AST:	Aspartate aminotransaminase	61
AGE:	Acute gastroenteritis	62

REFERENCES DECLARATION

References in this dissertation were inserted using Mendeley (reference software), with the application of the Cape Peninsula University of Technology – Harvard reference style, in accordance with the requirements of the Department of Nutrition and Dietetics.

SUMMARY

Background and motivation: The World Health Organisation (WHO) uses the term severe acute malnutrition (SAM) to describe children under five years who are severely malnourished and present with severe wasting, classified by weight-for-length/height <-3 standard deviation (SD) according to the WHO growth standards or mid-upper arm circumference (MUAC) <11.5 cm, or bilateral pitting oedema. Children with complicated SAM require hospitalisation and urgent care including nutritional intervention. Too rapid introduction of nutrition can result in refeeding syndrome (RFS), a life-threatening complication with onset usually within five days of starting nutritional therapy. Yet, RFS remains underdiagnosed because a universally agreed definition does not exist, and many physicians are unaware of the syndrome. Moreover, current WHO guidelines for the dietary treatment of SAM, and published guidelines for the prevention of RFS in the clinical setting, are incongruent. Very few studies to date have investigated the incidence of RFS in SAM, particularly in relation to a high prevalence of human immune deficiency virus (HIV). This study, therefore, aimed to identify the incidence of RFS, as well as factors that may be associated with the onset of RFS, among children with SAM in a South African public health setting.

Methods: A retrospective analytical cohort study of children aged 0 – 59 months admitted with SAM to Rahima Moosa Mother and Child Hospital, Johannesburg, from 1 October 2014 to 31 December 2018, was conducted. Among the hospital files that could be retrieved from the archives, the diagnosis of SAM according to the WHO definition was confirmed for 126 files. In these participants, the occurrence of RFS, as characterised by a drop in blood phosphate levels by $\geq$0.16 mmol/L to a level $\leq$0.65 mmol/L, was noted. Biochemical and clinical features on admission, as well as dietary intake, were compared between participants who developed RFS and those who did not, using Fisher's exact, Chi-square or Kruskal-Wallis tests as appropriate. P-values <0.05 were considered statistically significant.

Results: The incidence of RFS in the sample (63% male; median age: 34 months) was 8.7% (n=11) of whom 18.2% died. The development of RFS was statistically significantly associated with hypophosphataemia, hypokalaemia, hyponatraemia, dehydration, international normalised ratio (INR) >1.7, and urinary tract infection (UTI)

on-admission, and longer length of hospitalisation, but not with being HIV positive. HIV-exposure was, however, borderline statistically significant and diarrhoea had a trend towards significance on admission in participants who later developed RFS. Findings on protein and energy intakes were inconclusive as the grade of oedema, which influences the dietary requirements, was not recorded consistently in the hospital files. Most participants developed RFS after day five of hospitalisation, which is inconsistent with the usual timing of the development of RFS. Most participants were receiving F-75 substitutes (standard, soy or extensively hydrolysed infant formula with or without additional modular supplementation) during the initial phase of dietary treatment, thus high protein intake in oedematous participants may have contributed to the development of RFS in this study.

Conclusions and recommendations: This study confirms the occurrence of RFS in patients with SAM and identifies several biochemical and clinical features present on admission that may aid in the identification of high-risk patients. This information may assist in the revision and standardisation of feeding protocols. Further investigation into risk factors which might predispose a child with SAM to develop RFS may help in reducing the incidence of RFS and the concurrent risk of death that it poses and, therefore, assist with the WHO's goal to reduce the mortality of children under the age of five. Physicians, nurses and dietitians should be educated on RFS in order to diagnose and treat patients with SAM more effectively. The study highlights the importance of identifying and recording the grades of oedema in children with complicated SAM, which is vital for prescribing the correct dietary requirements. It also highlights the need for dietitians and other healthcare professionals to follow the WHO guidelines for the treatment of SAM, and use F-75 substitutes with great caution as their protein content is higher and their micronutrient composition is lower compared to F-75.

Keywords: Refeeding syndrome, severe acute malnutrition, hypophosphataemia, oedema, malnutrition, paediatrics, energy intake, protein intake, refeeding syndrome risk factors, South Africa

CHAPTER 1: BACKGROUND AND MOTIVATION FOR THE STUDY

1.1 Introduction

Severe acute malnutrition, previously known as marasmus or kwashiorkor, is a term used by the WHO for children under five years of age who are severely undernourished and who present with either severe wasting (weight-for-length/height <-3 SD or MUAC <11.5 cm), or the presence of bilateral pitting oedema (WHO, 2013b:2; Lenters et al., 2016:206; Mbethe & Mda, 2017:1). Children with SAM receiving nutritional intervention are at risk of developing RFS, adding to the already high death rates associated with SAM (Namusoke et al., 2016:551; Rytter et al., 2017:494), Refeeding syndrome is a complication caused by fluid and electrolyte imbalances that arise after the re-introduction of food in a malnourished or starved patient, and was first recognised during World War Ⅱ when starved prisoners of war developed cardiac failure after the reintroduction of food (Tresley & Sheean, 2008:2105).

Refeeding syndrome mainly occurs within the first two to five days after reintroduction of nutritional therapy and patients who develop RFS have poorer outcomes and have a significantly increased risk of death (Parli et al., 2014:197; Skipper, 2012:35; Friedli et al., 2020b:140). RFS is treatable, but is generally underdiagnosed due to the lack of awareness and understanding of the syndrome by physicians and is, therefore, undertreated (Gariballa, 2008:604; Friedli et al., 2020b:138). In South Africa, the factors associated with the development of RFS are especially important owing to the high prevalence of the HIV and tuberculosis (TB) which contribute to the development of malnutrition as well as high infant and childhood death rates (De Maayer & Saloojee, 2011:1; Biggs, 2013:175). According to Tickell & Denno (2016:647), addressing SAM in a setting with a high prevalence of HIV and TB, whilst preventing RFS, poses specific challenges that have not been well researched.

1.2 Severe acute malnutrition

Malnutrition occurs in different forms, including undernutrition (underweight, wasting and stunting), overnutrition (overweight and obesity), as well as micro-nutrient deficiency (WHO, 2020a). This study focused exclusively on malnutrition in the form of undernutrition, specifically occurring as severe wasting. A child who is wasted is "too thin for his or her height" (UNICEF/WHO/World Bank Group, 2020:2). Wasting occurs when weight loss arises rapidly, or due to failure to gain weight owing to insufficient dietary intake and/or the presence of disease (UNICEF/WHO/World Bank Group, 2020:2). Severe wasting (weight-for-length/height <-3 SD or MUAC <11.5 cm), with or without the presence of nutritional oedema is defined as SAM (Williams & Berkley, 2018:S32). Children who are wasted, and especially those with SAM, have suppressed immune systems, are inclined to have delays in their long-term development and are at an increased risk of dying (UNICEF/WHO/World Bank Group, 2020:2).

Children with SAM can either be clinically well and, therefore, have a good appetite and have no signs of infection, or their situation may be more complicated when they present with infection, severe dehydration, hypoglycaemia, hypothermia, metabolic disturbances, vomiting, severe oedema, severe anaemia and/or appetite loss (Cloete, 2015:2; Williams & Berkley, 2018:S32). Furthermore, children with severe oedema also often present with dermatosis which can easily become infected (Cloete, 2015:1). In addition, children with complicated SAM need hospitalisation and require treatment (Cloete, 2015:2; Williams & Berkley, 2018:S32). Various studies have identified certain biochemical markers that predict a poorer outcome and even death in children admitted with SAM such as low phosphate on day two of hospitalisation especially in oedematous children, C-reactive protein (CRP) >15 mg/L, an INR >1.7 in oedematous children, and thrombocytopaenia in children with HIV infection (Tadesse et al., 2010:18; De Maayer & Saloojee, 2011:563; Rytter et al., 2017:494). Furthermore, clinical signs and conditions that have been associated with a negative outcome in children with SAM include pallor, decreased consciousness, a capillary refill of more than two seconds, oral thrush, shock and presence of HIV infection. (De Maayer & Saloojee, 2011:560;.Rytter et al., 2017).

Globally, the prevalence of SAM has only decreased by 11% in the last 20 years and remains significantly associated with death (Desyibelew et al., 2020:1). Almost 45% of deaths worldwide in children below five years are related to undernutrition (WHO, 2020a). Worldwide in 2019, wasting occurred in 47 million children (6.9%) under five years, of whom 14.3 million had severe wasting, and thus suffered from SAM, and 144 million (21.3%) were stunted, therefore, had a low length/height-for-age. The statistics in Africa in 2019 show that wasting occurred in 12.7 million children below five years, of whom 3.5 million had severe wasting, and thus suffered from SAM, and 57.5 million were stunted. Furthermore, in Southern Africa, 0.2 million children under five years were wasted and two million were stunted (UNICEF/WHO/World Bank Group, 2020). Additionally, the novel COVID-19 virus which was declared a pandemic and a public health crisis on 11 March 2020 by the WHO, and which triggered a worldwide economic and social crisis and could seriously affect the nutritional status and mortality rate of children in low- and middle-income countries (WHO, 2020b; Headey et al., 2020). Furthermore, Headey et al., (2020) predict that as a result of the disturbances in economic, food and health systems as a result of COVID-19, all forms of malnutrition are likely to worsen.

Currently, patients admitted to Rahima Moosa Mother and Child Hospital with SAM are treated according to the WHO 10-step protocol for the in-patient management of severely malnourished children (Appendix A). This study focused on the nutritional management of SAM, which is outlined in steps seven and eight of the protocol namely: “begin cautious feeding” (stabilisation and transition phase) and “increase feeding to recover weight loss, also known as “catch-up growth feeding” (rehabilitation phase) (WHO, 2009:42; WHO, 2013a:209-210).

The initial phase of the WHO protocol aims to stabilise the patient, which includes providing a milk-based formula that is low in protein and treating the patient for medical complications. Subsequently, an intermediate practice called transition phase feeding is used to transition from the stabilisation phase to the rehabilitation phase and involves slowly increasing energy intake to reduce the risk of RFS. Implementation of this practice appears to reduce the risk of RFS (WHO, 2013b:41). Lastly, the rehabilitation phase includes providing a milk-based formula higher in protein and energy, with the purpose of achieving catch-up growth (WHO, 2013b:40).

1.3 Refeeding syndrome

The leading causes of death in children who are malnourished are diarrhoea, pneumonia, measles and malaria, as well as metabolic abnormalities which include RFS and hypoglycaemia (Bhutta et al., 2017:2). RFS may develop when nutrients, especially those low in phosphorous and magnesium and high in carbohydrates, are introduced after periods of starvation (Hother et al., 2016:2). During the catabolic state of starvation, energy is obtained by breaking down protein and fat through gluconeogenesis and ketogenesis, instead of from stored glycogen synthesised from the consumption of carbohydrates (Friedli et al., 2018). Therefore, after periods of starvation, the sudden influx of nutrients causes energy metabolism to shift from catabolism to anabolism, thus from fat and protein to carbohydrate metabolism. In turn, this results in a surge in the release of insulin, leading to the rapid movement of electrolytes, notably phosphorous, magnesium and potassium from the extracellular compartment into the cells (Namusoke et al., 2016:551; Rytter et al., 2017:494). The resultant fluid and electrolyte disturbances which manifest as hypophosphataemia, hypomagnesaemia and hypokalaemia may lead to circulatory failure, respiratory failure, abnormal renal function, liver dysfunction, hyperglycaemia, various other metabolic abnormalities, and even death (Crook, 2014:1450; Parli et al., 2014:197; Hother et al., 2016:2; Rytter et al., 2017:494). Furthermore, research has begun to identify factors that are associated with RFS in SAM, such as diarrhoea, septic shock, oedema, nasogastric-tube feeding, HIV infection, dermatosis, hypocalcaemia, hypokalaemia and hypomagnesaemia (Afzal et al., 2002:516; Bhutta et al., 2017:11; Mbethe & Mda, 2017:6; Okinyi, 2018:69). Namusoke et al., (2016:557), have also emphasized that F-75 substitutes should be used cautiously as their mineral content may be inadequate and could, therefore, precipitate electrolyte abnormalities.

Notably, as yet, a standardised definition for RFS has not been reached (da Silva et al., 2020:179). Generally, in practice, the two major characteristics that signal the development of RFS are considered to be hypophosphataemia, and the development of the syndrome within two to five days after initiating feeding (Mehanna et al., 2008:1495; Parli et al., 2014:197; Skipper, 2012:35,38). Skipper (2012:34,38) questioned whether RFS should be differentiated from refeeding hypophosphataemia, noting that the syndrome does not consistently present with the same biochemical and clinical irregularities. Also, hypophosphataemia can have aetiology other than RFS,

for example, Rady & Mohamed (2014:4) have linked hypophosphataemia to the use of diuretics or steroids, and the onset of sepsis. Consequently, in 2020, two consensus definitions were published. Firstly, Friedli et al. (2020b:140) distinguish between two types of RFS namely manifest RFS (electrolyte disturbances with clinical symptoms) and imminent RFS (electrolyte disturbances) occurring within 72 hours after the initiation of feeds. The electrolyte disturbances include a drop in phosphate by >30% or a value <0.6 mmol/L, or the presence of two of the following: phosphate <0.80 mmol/L, potassium <3.5mmol/L, and/or magnesium <0.75 mmol/L. Lastly, the ASPEN consensus definition incorporates varying degrees of RFS indicated by a drop in one or more of the following, namely phosphorus, potassium, and/or magnesium, within five days after initiating feeds. Thus, mild RFS occurs if these biochemical values drop by 10%–20%. Moderate RFS occurs if they drop by 20%–30% and severe RFS occurs if they drop by >30% with or without the presence of organ dysfunction (severe RFS) (da Silva et al., 2020:189).

1.4 Problem statement

Children who are admitted to hospital for SAM frequently have poor outcomes owing to reasons that are often unexplained (Rytter et al., 2017:494). Refeeding syndrome is potentially a significant contributing factor to mortality in children with SAM. The WHO protocol for the management of SAM in children between 0 – 59 months of age stipulates a transition phase of treatment specifically to address and prevent RFS(WHO, 2013b:41). However, the true incidence of RFS related to SAM remains unknown due to a paucity of studies in this population (Mbethe & Mda, 2017), which is no doubt complicated by the absence of a universally accepted definition of RFS (Mehanna, Moledina and Travis, 2008:1495). Furthermore, researchers such as Tickell and Denno (2016:648) have questioned the evidence for the WHO treatment guidelines for the inpatient management of children with SAM. They expressed the need for more clinical and epidemiological research to support and improve treatment guidelines. The guideline development group for the WHO protocol also noted a lack of research to inform transition feeding guidelines (WHO, 2013b:41). Furthermore, of concern is that physicians, especially inexperienced ones, have trouble recognizing

and treating RFS as their awareness of the syndrome is very low (Friedli et al., 2020b:138).

More research is thus required to gain insight into the incidence and characteristics of RFS in SAM, particularly in the South African setting where very little is known regarding the impact of HIV and TB as comorbidities in the management of SAM, and how this relates to the risk of developing RFS. Also, very little information is available on the specific risk factors that may predispose a severely malnourished child to develop RFS in a population with a high prevalence of HIV and TB.

This retrospective study of hospital files and nutrition care records (NCRs), therefore, aimed to determine the incidence and onset of RFS, characterised by hypophosphataemia, in a South African public hospital setting among infants, 0 – 59 months, diagnosed with SAM. The study also hoped to identify biochemical, medical and dietary factors that may be associated with the onset of RFS in these infants. These findings will add to the sparse existing knowledge on the subject and contribute to the early identification of infants with SAM who are at an increased risk for developing RFS. Such findings may be useful to inform the development of a more comprehensive and integrated feeding protocol for patients diagnosed with SAM.

1.5 Aim and objectives

The aim and objectives of this study are as follows:

1.5.1 Aim

This study aimed to describe the incidence and onset of RFS, characterised by hypophosphataemia, and biochemical abnormalities, clinical signs, medical complications and dietary-related factors that may be associated with the development of RFS in children aged 0 – 59 months diagnosed with SAM, based on a retrospective audit of hospital files and NCRs.

1.5.2 Objectives

To achieve the aim of the study, the following variables were documented from the hospital files and NCRs for each participant:

i. Socio-demographic and clinical profiles (date of birth, age, gender, country of origin, ethnicity, date of admission, date of discharge, date of death and length of hospital stay);

ii. Anthropometry and clinical data to confirm the diagnosis of SAM (weight and length/height to calculate weight-for-length/height, mid-upper arm circumference (MUAC) and the presence of bilateral pitting oedema;

iii. In participants with confirmed SAM:

   a. Biochemistry (blood levels of phosphate, potassium, magnesium, calcium, sodium, albumin, CRP, urea, creatinine, liver enzymes, haemoglobin, platelet count and INR);
   b. Clinical signs and medical complications on day one of hospitalisation; and
   c. Dietary prescription analysis (energy and protein intake per kilogram) prescribed by the physician or dietitian, phase of feeding (stabilisation, transition or rehabilitation) and type of feed/formula that was prescribed for the first five days during which RFS is most likely to have occurred. If RFS occurred after this period, energy and protein intake was recorded for the full duration until the day that the biochemical abnormality occurred;

iv. For participants for whom the diagnosis of SAM could be confirmed, the above variables were compared between those who developed RFS and those who did not develop with RFS during their documented hospital stay.

1.6 The layout of the dissertation

Chapter 1:

Overview and motivation for the study as well as the problem statement and aim and objectives;

Chapter 2:

Literature review including an overview of malnutrition, refeeding syndrome and the risk of refeeding syndrome in severe acute malnutrition;

Chapter 3:

Study design, study population and sampling, measurements, variables and operational definitions, techniques, limitations, validity and reliability, data collection, pilot study, statistical analysis, ethical approval and permission;

Chapter 4:

Article 1: Refeeding syndrome characterised by hypophosphataemia in children aged 0 – 59 months diagnosed with severe acute malnutrition in a South African setting;

Chapter 5:

Article 2: Dietary factors associated with refeeding syndrome in children with severe acute malnutrition; and

Chapter 6:

Conclusions, and recommendations for future research, and a consideration of the limitations of the study.

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CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Severe acute malnutrition, previously known as marasmus and kwashiorkor (Lenters et al., 2016:206) is defined by severe wasting i.e. weight-for-length/height <-3 SD or MUAC <11.5 cm, classified according to the WHO growth standards released in 2006, and/or the presence of bilateral pitting oedema and is a significant health problem which contributes to high childhood mortality throughout the world (WHO, 1999:4; WHO/UNICEF, 2009:2; WHO, 2013b:10; Rytter et al., 2017:494; Williams & Berkley, 2018:S32). Globally, undernutrition is the cause of about 45% of deaths in children below five years (WHO, 2020b). The WHO has paid much attention to SAM and has developed comprehensive guidelines for the treatment of SAM. Despite these guidelines, some children treated for SAM, still develop RFS, a life-threatening condition that adds to the high mortality-rates of this vulnerable population. Research on RFS has been complicated by the fact that a universally accepted definition for the syndrome does not exist (Friedli et al., 2017:158; da Silva et al., 2020:179).

This chapter firstly reviews the literature on the aetiology of malnutrition in children, and then focuses on the classification and dietary treatment guidelines for the management of SAM. Secondly, the diverging definitions of RFS, the pathophysiology, incidence and aetiology, as well as the nutritional management of RFS, are reviewed. Thirdly, the occurrence of RFS in SAM is explored.

2.2 The aetiology of malnutrition

Malnutrition is a multifactorial term that incorporates both overnutrition and undernutrition. Overnutrition refers to overweight and obesity, whereas undernutrition refers to many conditions including micronutrient deficiencies, acute malnutrition and chronic malnutrition (Lenters et al., 2016:205). Sobotka (2012, referenced by Cederholm et al. (2017:51)) refers to malnutrition as “a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease”.

2.2.1 Disease and non-disease-related malnutrition

While the WHO and the United Nations Children's Fund (UNICEF) have focused much attention on providing guidelines for the recognition and treatment of malnutrition in children, it is essential to realise that malnutrition affects people in all stages of life and different settings due to different reasons that may co-occur.

Recognising a need for a universal, overarching classification and terminology system to guide the development of clinical treatment guidelines for malnutrition, an expert work-group of the European Society for Parenteral and Enteral Nutrition (ESPEN), developed an aetiology-based definition of malnutrition (Cederholm et al., 2017). Accordingly, malnutrition may occur secondary to disease states referred to as disease-related malnutrition (DRM) or can occur due to not having enough to eat, referred to as non-disease related malnutrition (non-DRM). Two types of DRM are recognised. Firstly, some chronic diseases and ageing may decrease or derange food intake, digestion, absorption or metabolism and cause DRM in the absence of inflammation. Secondly, DRM may be driven by inflammation that results from the metabolic stress response to acute injury, infection, acute disease, or some chronic diseases, all of which can result in loss of weight and muscle, or cachexia (Cederholm et al., 2017). The framework illustrated in Figure 2.1 provides a schematic representation of malnutrition. Whereas DRM is the main form of malnutrition which occurs in affluent societies, ESPEN recognises that non-DRM is still a significant cause of malnutrition in poor and developing countries (Cederholm et al., 2017:53).

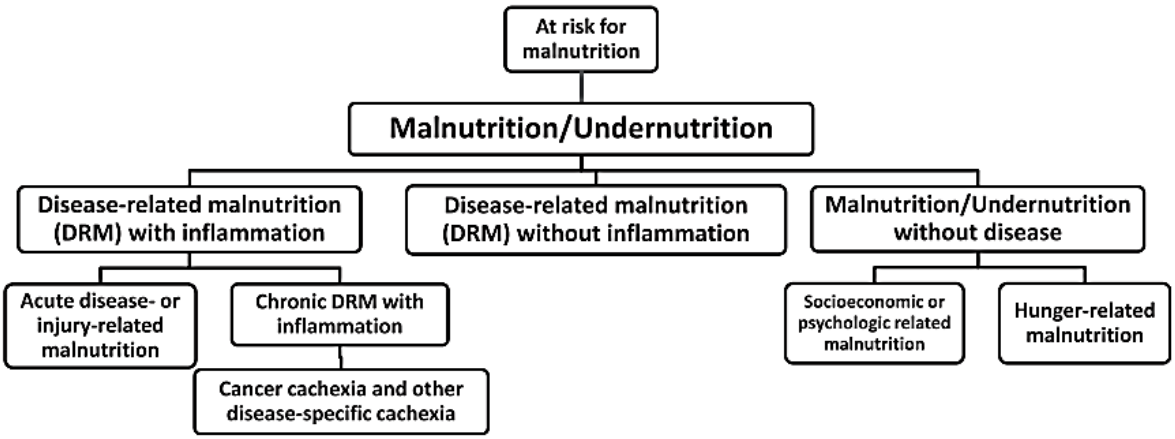
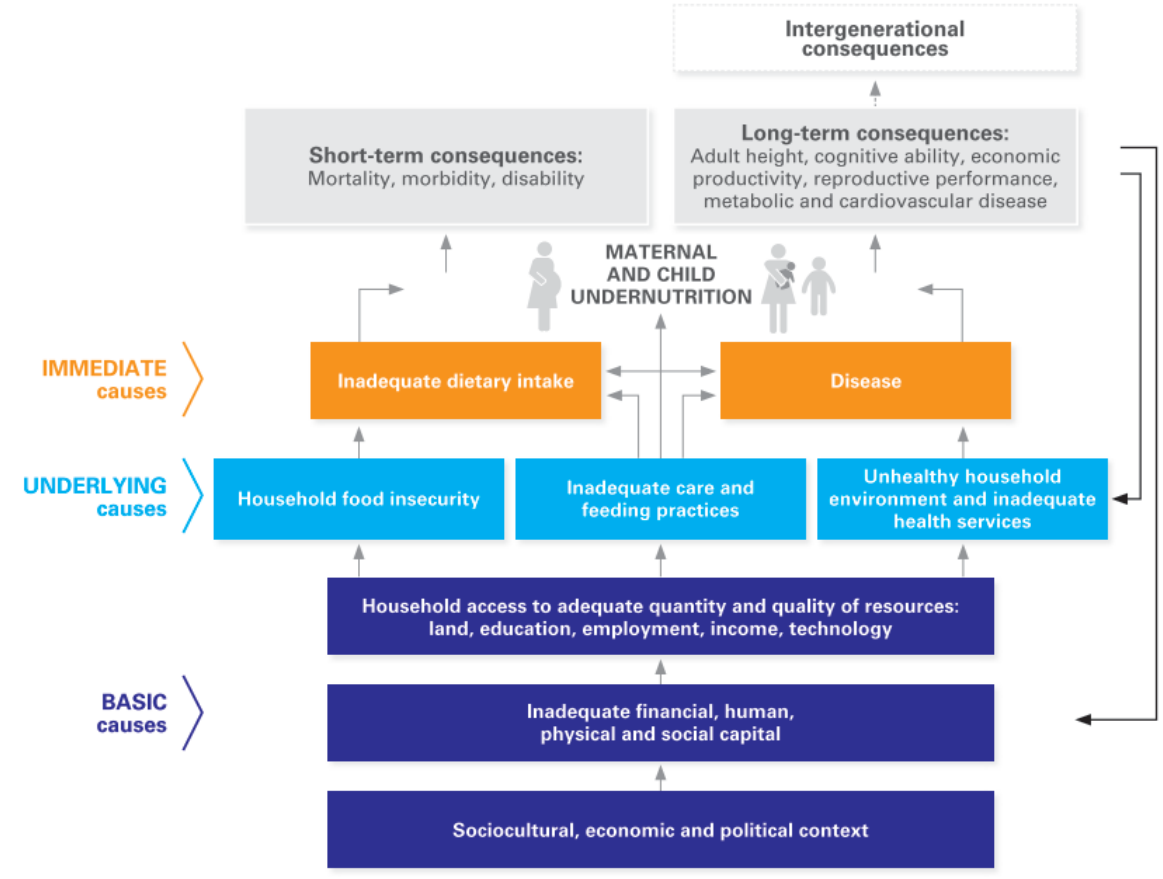


Figure 2.1: Diagnoses tree of malnutrition; from at risk for malnutrition, basic definition of malnutrition to aetiology-based diagnoses
(Cederholm et al., 2017:53)

2.2.2 Aetiology of non-disease related malnutrition

Concerning the specific aetiology of what the ESPEN framework refers to as non-DRM, the UNICEF conceptual framework for malnutrition (Figure 2.2), developed in 1990, is still widely used (UNICEF, 2013:3). This framework captures and explains the basic, underlying and immediate causes of childhood undernutrition and how these are linked (Lenters et al., 2016:206). The two main causes of undernutrition are inadequate dietary intake and/or the presence of disease, and are broadly influenced by food security, inappropriate child care practices, lack of health services and unhealthy environments (UNICEF, 2013:3). Notably, undernutrition not only increases the possibility of developing infections but also increases the severity thereof and prolongs the recovery process (UNICEF, 2020). Therefore, "the interaction between undernutrition and infection creates a potentially lethal cycle of worsening illness and deteriorating nutritional status"(UNICEF, 2013:3).



The black arrows show that the consequences of undernutrition can feed back to the underlying and basic causes of undernutrition, perpetuating the cycle of undernutrition, poverty and inequities.

Figure 2.2: Conceptual framework of the determinants of child undernutrition (UNICEF, 2013:4)

To obtain optimal nutritional status, parents/caregivers of children need access to the following: affordable and good quality, nutrient-dense food; family resources such as money and knowledge; access to satisfactory health services; an environment with sanitation and clean water; good hygiene practices and proper maternal and child-care (UNICEF, 2013:3; UNICEF, 2019:97).

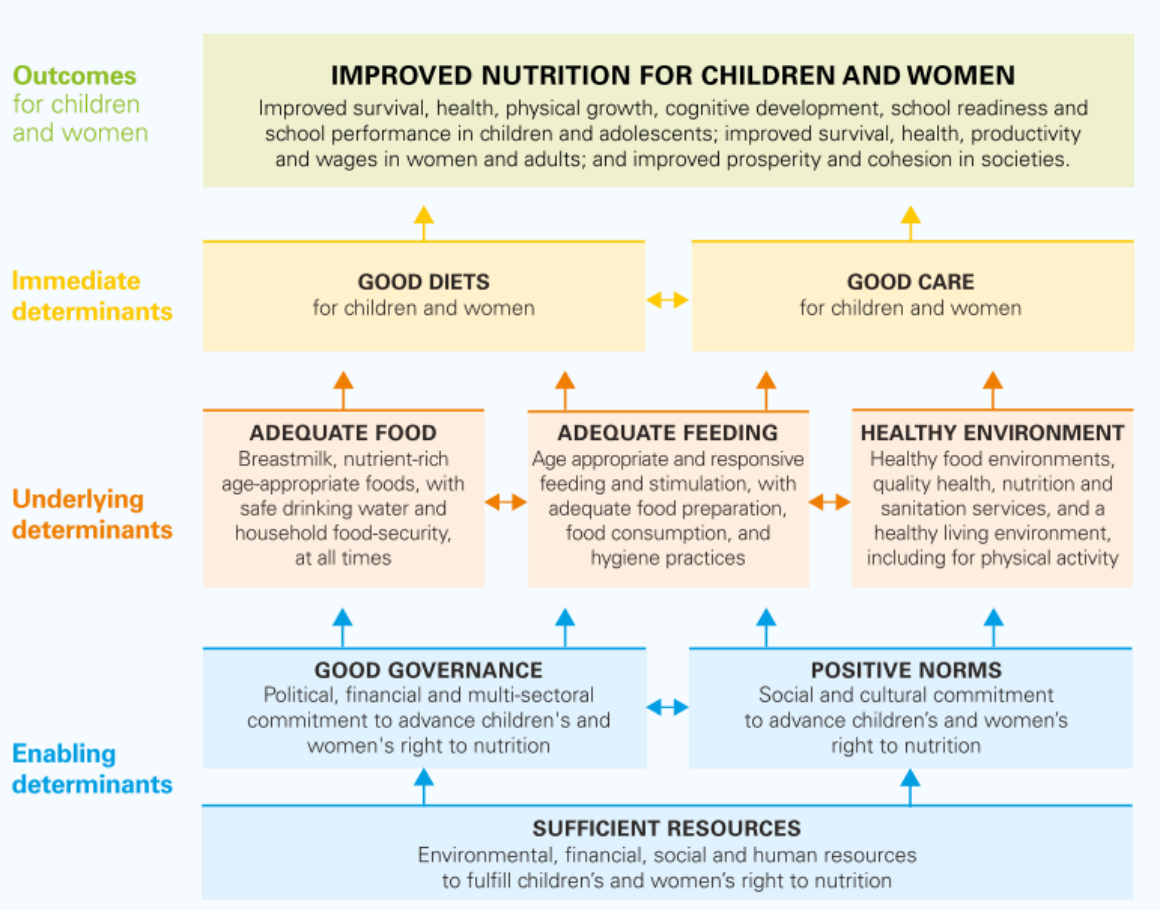


Figure 2.3: Conceptual Framework of the Determinants of Maternal and Child Nutrition (UNICEF, 2019:97)

Furthermore, Black et al. (2020) have proposed a revised conceptual framework represented in Figure 2.4. Their proposal is founded on the Sustainable Development Goals that recognise, in order to have a healthy, prosperous, peaceful and independent future, children need not only to survive, but also to thrive. To achieve this, in addition to good nutrition and health, children need environments that enable them to thrive such as supportive families, safe and secure communities and access to education which are underpinned by stable politics, economics and environmental awareness (Black et al., 2020:e766-e767).

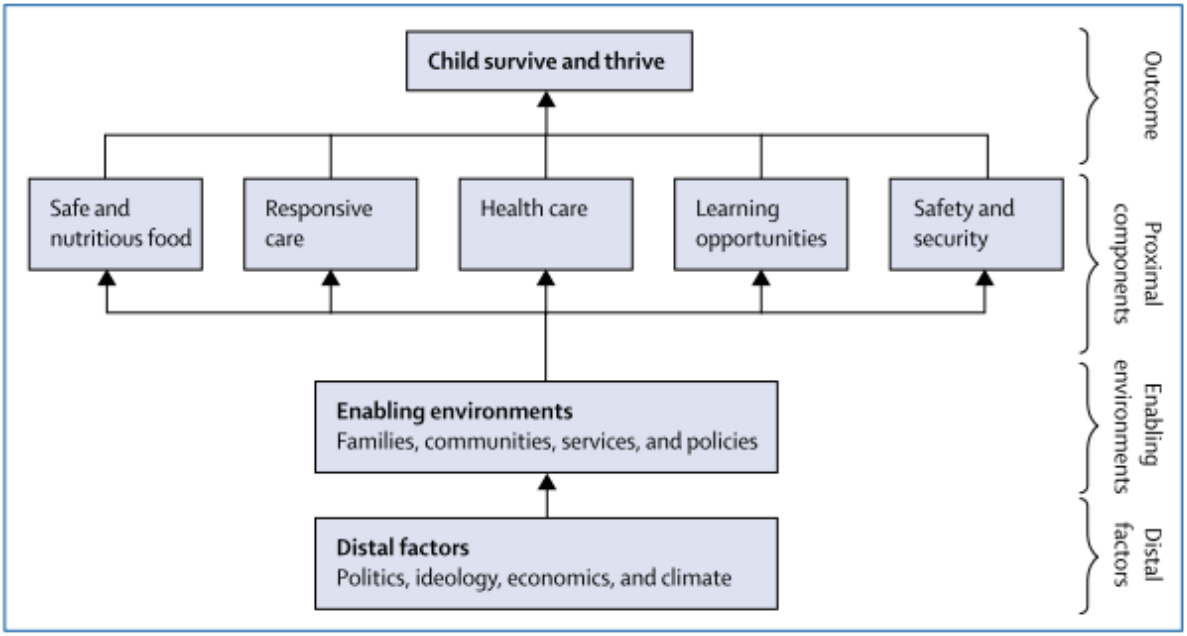


Figure: **Conceptual framework of children surviving and thriving**
The revised conceptual framework of malnutrition expands to survive and thrive by including safe and nutritious food, responsive care, health-care learning opportunities, and safety and security.

Figure 2.4 Conceptual framework of children surviving and thriving (Black et al., 2020:e766)

2.2.3 Definitions and classifications of severe malnutrition among children under five years

Severe malnutrition in children has been defined in different ways and has undergone many re-classifications over the years, which has influenced the assessment and treatment thereof (Picot et al., 2012:2-3). This section outlines the various definitions and classifications used to diagnose SAM in children below five years.

2.2.3.1 Historical definitions of severe childhood malnutrition

Terminology to describe and define severe malnutrition has evolved. The terms that have been used to describe children who are severely wasted with or without oedema thus far are kwashiorkor, marasmus, protein malnutrition, protein-energy malnutrition (PEM), severe malnutrition and SAM. (Picot et al., 2012:5).

Protein malnutrition and PEM were terms first described in children and were derived from the name kwashiorkor, which was first described by Dr Cicely Williams, in1930 (Waterlow, 1997:3). Earlier descriptions of the same condition were, however, first

identified in Latin America where it was called multi-deficiency syndrome, and in Europe where it had been known as flour dystrophy (Golden, 2010:667). After the Second World War, the WHO and the Food and Agriculture Organisation (FAO) investigated the rate of occurrence and cause of kwashiorkor in Africa, Brazil and Central America. The Brazilian investigation highlighted the difference between kwashiorkor and marasmus (semistarvation), a historical term, and noted that a mixed form of these two conditions had also been occurring. The WHO and FAO then concluded that kwashiorkor developed due to a protein deficiency, and thus re-named it protein malnutrition (Waterlow, 1997:4).

Protein malnutrition was further investigated during the 1970s in various dietary surveys that determined that young children consumed adequate amounts of protein, but inadequate amounts of energy. Furthermore, the occurrence of marasmus was more common than kwashiorkor. Gopalan then argued that children consuming food similar in quantity and quality developed both marasmus and kwashiorkor. Therefore, PEM became the new term to incorporate the range of conditions, namely marasmus which indicated a total energy deficiency, and kwashiorkor which indicated a relative protein deficiency (Waterlow, 1997:4). Protein-energy malnutrition is, therefore, a term that includes two primary forms of severe malnutrition namely, kwashiorkor and marasmus, and a mixed form known as marasmic-kwashiorkor (WHO, 1981:7), mainly occurring in developing countries due to socioeconomic, political and environmental factors that affect food supply. (Grover & Ee, 2009:1055). Marasmus is characterised by muscle wasting and decreased subcutaneous fat stores, and children appear clinically emaciated and present with weakness, lethargy, hypothermia, bradycardia and hypotension (Alberda et al., 2006:420; Grover & Ee, 2009:1059). In contrast, kwashiorkor can develop more rapidly and is characterised by oedema, dermatosis, depigmentation of the hair and a distended abdomen (Alberda et al., 2006:420; Grover & Ee, 2009:1059).

After extensive research on starvation during and after the Second World War, malnutrition in all its forms was treated with diets high in protein and energy but recovery rates did not improve (Golden, 2010:668). After realising and researching the detrimental effects of treating malnutrition with diets high in energy, low protein diets were introduced into clinical practice which decreased mortality rates (Golden,

2010:668). These insights led to a hypothesis that kwashiorkor was caused by a lack of antioxidant nutrients also known as Type I nutrients (Golden, 2010:667-668). After experimentation, Golden devised a theory that one of the leading causes of appetite loss is an imbalance in nutrient intake. The theory proposed that loss of appetite in children from traditional weaning foods is due to the normally low content of certain nutrients in these foods. Loss of appetite; owing to nutrient deficiency will, therefore, decrease energy intake. However, this deficit cannot be corrected by adding extra energy in the form of carbohydrates and fat (Golden, 2010:669). Owing to these interpretations, Golden's theory of Type I and Type II nutrients was postulated. Type I nutrients, also known as functional nutrients e.g. iron, thiamine and vitamin A among others are involved in the body's metabolic functions and present with specific clinical signs. Kwashiorkor would possibly then be caused by Type I nutrient deficiencies (Golden, 2010:667; Golden, 1996). Type II nutrients, also known as growth nutrients, for example, protein, zinc and potassium among others, present with delayed growth which may result in conditions like marasmus, characterised by wasting and stunting. (Golden, 2010:669; Golden, 1996). One could, therefore, conclude that if marasmus is not caused by an energy deficiency and kwashiorkor is not caused by protein deficiency, then the term PEM is a misleading term that has led to inappropriate nutritional management (diets high in energy and protein), and probably the death of many children in the past (Golden, 2010:669). As a result, the terms marasmus and kwashiorkor have since been replaced by the term SAM classified by the WHO (Lenters et al., 2016:206), which will be discussed in detail below.

2.2.3.2 Evolution of classifying severe malnutrition in children

Malnutrition can develop over a prolonged period of time or can occur more rapidly over a shorter period of time. Inadequate absorption or intake of nutrients over a prolonged period of time manifests as chronic malnutrition and is indicated by stunting (being too short for one's age). Stunting affects children's development and also their economic potential in adulthood (Lenters et al., 2016:205). Conversely, a rapid decrease in food intake and food quality manifests as acute malnutrition which is indicated by wasting (being too thin for one's height) (Lenters et al., 2016:205). Furthermore, acute malnutrition occurs in varying degrees of severity (UNICEF, 2014:vii). The degree of severity is associated with an increased risk of death (Lenters

et al., 2016:208). Various classification systems based on different anthropometric indicators and clinical features have been used to describe the severity of malnutrition in infants and children below five years (Picot et al., 2012:4). The various classifications are summarised in Table 2.1.

Firstly, the Gómez classification introduced in 1956, classified malnutrition into different degrees of severity based on weight-for-age. Thereafter, in 1969 the Wellcome Trust International Working Party classification was developed which classified malnutrition based on whether the child had oedema or not and according to the child's weight as a percentage of the Boston standard (Shakir, 1975:70; Picot et al., 2012:4; Grover & Ee, 2009). Then in 1971, Seoane & Latham, (1971:103) recommended the use of age, weight and height to differentiate between mild and moderate PEM, as using only one parameter, such as Gómez's classification, could be misleading. Seoane & Latham (1971:103), therefore, compared age, weight and height parameters with standards and defined three groups of malnutrition namely: 'current acute short duration malnutrition' (normal height-for-age, low weight-for-height and low weight-for-age); 'past chronic malnutrition' (normal weight-for-height, low weight-for-age and low height-for-age); and 'current long duration malnutrition' (low weight-for-age, low height-for-age and low weight-for-height).

Table 2.1: Classifications of malnutrition (Grover & Ee, 2009; Picot et al., 2012)

Classification of malnutrition	Definition	Reference	Grading	
Gómez	Weight below % median weight-for-age[1]	90–110	Normal	
		75–89	Grade I: mild malnutrition	
		60–74	Grade II: moderate malnutrition	
		< 60	Grade III: severe malnutrition	
Wellcome Trust International Working Party classification	Weight-for-age (% of reference)[2]	60–80	Kwashiorkor (with oedema)	Undernourished (without oedema)
		< 60	Marasmic kwashiorkor (with oedema)	Marasmus (without oedema)
Waterlow et al.	% weight-for-height	> 90	Normal	
		80–90	Mild wasting	
		70–80	Moderate wasting	
		< 70	Severe wasting	
	% height-for-age	> 95	Normal	
		90–95	Mild stunting	
		85–90	Moderate stunting	
		< 85	Severe stunting	
WHO (wasting)	Median weight-for-height	-3 ≤ SD[3] <-2	Moderate wasting	
		<-3 SD	Severe wasting	
WHO (stunting)	Median height-for-age	-3 ≤ SD <-2	Moderate stunting	
		<-3 SD	Severe stunting	
Kanawati	MUAC[4] divided by occipitofrontal head circumference	<0.31	Mild malnutrition	
		<0.28	Moderate malnutrition	
		<0.25	Severe malnutrition	
Cole (grade of thinness)	BMI-for-age	<-1 SD	Grade 1	
		<-2 SD	Grade 2	
		<-3 SD	Grade 3	

[1] Weight is compared with that of a normal child (50th percentile) of the same age. Percent of reference weight-for-age = (patient with a normal weight of the same age) × 100;
[2] Boston reference weight (median/50th percentile) for a child with a normal weight of the same age
[3] Standard deviation
[4] Mid-upper arm circumferences

In 1977, Waterlow and his colleagues recommended a classification which identified varying degrees of wasting and stunting based on weight-for-height and height-for-age SDs below the median (Grover & Ee, 2009:1057; Picot et al., 2012:4-5). In 1983, the WHO implemented the US National Center for Health Statistics (NCHS) classification which was used across the globe as a reference to classify a child's weight and height (Grover & Ee, 2009:1057). The WHO has since modified the classification to identify underweight, wasting and stunting based on z-scores/SD below the median on the new 2006 WHO growth reference standards. The reason why the WHO changed the reference criteria is because the NCHS criteria were developed from an "ethnically homogenous population, which likely does not represent

developing world countries, inclusion of bottle-fed infants, and the assumption that all children of given height will have the same average weight regardless of age" (Grover & Ee, 2009:1057). The 2006 WHO reference standards were established based on the growth of breastfeeding children from many different ethnic backgrounds and in many different countries worldwide. Furthermore, research has indicated that using the WHO reference standards increases the prevalence of malnutrition compared to using the NCHS reference standards (Grover & Ee, 2009:1057). In addition, MUAC used as a substitution for weight, and head circumference as a substitution for height, have also been used as tools to assess malnutrition. Consequently, by dividing MUAC measurement by the head circumference measurement, the severity of malnutrition can be determined. Lastly, the degree of thinness has also been classified by the use of body mass index (BMI)-for-age (Grover & Ee, 2009:1058).

In conclusion, the use of weight-for-length/height as an anthropometric indicator for the diagnosis of SAM has progressively replaced the previous indicators based on weight-for-age. Weight-for-age is no longer considered an appropriate indicator for SAM as it does not distinguish children who are wasted from those who are stunted (short for age) and, thus, cannot differentiate "past nutritional history from current nutritional state" (Picot et al., 2012:3-4). Weight-for-age and length/height-for-age are more suitable indicators for chronic malnutrition, and weight-for-length/height is a more suitable indicator for acute malnutrition (Picot et al., 2012:4; Lenters et al., 2016:205).

2.2.3.3 The World Health Organisations's definitions and classifications of severe acute malnutrition

The WHO describes malnutrition as energy and/or nutrient intake that is either too little, too much or imbalanced (WHO, 2020b). Three forms of undernutrition have been identified by the WHO, namely underweight, wasting and stunting (WHO, 2020b). Firstly, underweight refers to a child having a low weight for his/her age. Secondly, "stunting refers to a child who is too short for his or her age" and can be associated with permanent physical and mental impairment (UNICEF/WHO/World Bank Group, 2020:2). Lastly, "wasting refers to a child who is too thin for his or her height" (UNICEF/WHO/World Bank Group, 2020:2). Wasting is characterised by rapid weight loss or insufficient weight gain, but is treatable. In addition, moderate and severe wasting increase the risk of mortality. Finally, it is necessary to point out that children

can present with two forms of malnutrition simultaneously, for example, a child may be stunted and wasted (UNICEF/WHO/World Bank Group, 2020:2).

i Classification of severe acute malnutrition in children 6 – 59 months of age

The WHO and UNICEF endorse three main criteria for the diagnosis of SAM in children 6 – 59 months of age which are summarised in Table 2.2. The three main criteria include the following (WHO/UNICEF, 2009:2):

- Weight-for-height <-3 SD using the current WHO growth standards published in 2006, indicate severe wasting. This criterion was chosen by the WHO and UNICEF for the following reasons, namely: children who have a weight-for-height <-3 SD are at an increased risk of death; gain more weight when receiving therapeutic feeds compared to other diets which result in earlier recovery; there are negligible numbers (<1%) of children <-3 SD in a well-nourished population, and children who are placed on the recommended protocols and receive suitable therapeutic feeds do not experience any identifiable risks or adverse effects.
- Mid-upper arm circumference <11.5 cm indicating severe wasting. Very few children between 6 – 59 months in a well-nourished population have a MUAC <11.5 cm according to the WHO growth standards for age. Children with a MUAC <11.5 cm are at an increased risk of death and for this reason the cut-off point for MUAC <11.5 cm to define SAM.
- The presence of bilateral pitting oedema. Oedema can occur in varying grades according to its severity namely: mild (+) which includes oedema of both the feet; moderate (++) which includes oedema of both the feet as well as the lower legs, hands or lower arms; and severe oedema (+++) which presents as full-body generalised oedema including oedema of both the feet, legs, arms, hands as well as the face (WHO, 2013b:4).

Table 2.2: Diagnostic criteria for SAM in children aged 6 - 59 months (WHO & UNICEF, 2009:2; WHO, 2013b:2)

Indicator	Indices	Cut-off
Severe wasting[1]	Weight-for-length/height[2]	<-3 SD[3]
Severe wasting[1]	MUAC[4]	<11.5 cm
Bilateral oedema[5]	Clinical sign	-

[1,5] Independent indicators of SAM that require urgent action
[2] Based on WHO Standards (www.who.int/child growth/standards) (WHO, 2016)
[3] Standard deviation
[4] Mid-upper arm circumference

Furthermore, SAM can be classified as complicated or uncomplicated (Williams & Berkley, 2018:S32). Children with uncomplicated SAM refer to children with appetite, and no signs of infection and are, therefore, clinically alert and well and can be treated as outpatients (Williams & Berkley, 2018:S32). Alternatively, children with complicated SAM have any of the following symptoms namely: severe oedema, poor appetite, lethargy, sickly appearance, medical complications (hypothermia, hypoglycaemia, respiratory tract infections, septic shock, skin infections, UTI, severe dehydration, or severe anaemia) and/or one or more Integrated Management of Childhood Illness danger signs i.e. “unable to drink or breastfeed; vomits everything; has had convulsions (more than one or prolonged >15 min); lethargic or unconscious; convulsing now” (WHO, 2013b:3,28; Williams & Berkley, 2018:S32) . These children need to be admitted for treatment (WHO, 2013b:3; Williams & Berkley, 2018:S32).

ii Classification of severe acute malnutrition in children below six months

Severe acute malnutrition in infants under six months is being identified more often (WHO, 2013b:60). Generally, SAM in this age group is caused by poor feeding, particularly breastfeeding practices, as well as causes like low birth weight, sepsis, chronic diarrhoea and underlying diseases (WHO, 2013b:60). It is unclear whether children under six months should be managed differently due to infants being different physiologically than older children (WHO, 2013b:60). Despite these differences, the WHO’s definition of SAM in infants under six months include (WHO, 2013b:63):

- Weight-for-length < -3 SD and/or
- Presence of bilateral pitting oedema

Furthermore, infants under six months diagnosed with SAM should be hospitalised if they arrive at casualty with any of the following complicating factors namely: serious clinical conditions or medical complications as discussed for infants 6 – 59 months of age; weight loss or poor weight gain; ineffective feeding; the presence of pitting oedema; and any existing medical or social issue needing assessment or support (WHO, 2013b:63).

2.2.4 The World Health Organisation guidelines on the nutritional management of severe acute malnutrition

The World Health Organisation first published guidelines to treat severe PEM in 1981. However, these guidelines were substantially revised as guidelines to manage severe malnutrition in 1999 (WHO, 1999:v). In 2009, the WHO and the UNICEF issued a joint statement on how to identify children with SAM using the new WHO growth standards (WHO & UNICEF, 2009:2). Current guidelines on the management of SAM are based collectively on the joint statements of the WHO and United Nations (UN) in 2007 and 2009 and on the revisions of the 2003 and 2013 WHO guidelines for the management of SAM (Tickell & Denno, 2016:1). In the current guidelines, no distinction is made between kwashiorkor and marasmus as the treatment is similar (WHO, 2013a:198). Appendix A summarises the WHO-10 step protocol and emergency treatment for the inpatient management of severely malnourished children (WHO, 2009:40-43). The aims of these guidelines are mainly to reduce malnutrition-related child mortality as well as to reduce stunting by 40% and decrease wasting to below 5% by 2025 (WHO, 2013b:9). Advances in the treatment of uncomplicated SAM have improved through the development of therapeutic ready-to-use food that can be used in the community, however, the treatment of complicated SAM has remained unchanged for the past two decades (Rytter et al., 2017:494). For this dissertation, step four, seven and eight will be discussed.

Children with SAM are likely to have electrolyte deficiencies including hypokalaemia and hypomagnesaemia which occur as a result of reductive adaptation during starvation(WHO, 2004:35-36). Therefore, supplementation of potassium and magnesium are included in step four of the WHO protocol (WHO, 2004:36). These additional electrolytes are already part of the F-75 formulation or can be individually prescribed by the doctor (WHO, 2009:41).

According to step seven and eight of the WHO guidelines, nutritional inpatient management of SAM is divided into two main phases i.e. the stabilisation (± two to seven days) and the rehabilitation phase with an intermediate transition from stabilisation to rehabilitation (Ashworth et al., 2003:10; Picot et al., 2012:7; WHO, 2013b:40). The initial phase aims to stabilise the patient and treat medical complications while providing a low protein formula, namely F-75, at 130 ml/kg/day for children without severe oedema and 100 ml/kg/day for children with severe oedema (WHO, 2013a:209; WHO, 2013b:40). The transition phase (when a child's appetite returns and medical complications are resolving) deals with the gradual change from the stabilisation phase to the rehabilitation phase to prevent the possibility of heart failure caused by RFS. This transition involves changing from F-75 to F-100 (a formula high in energy and protein) at the same initial volume of F-75, for 48 hours, and then increasing the volume by 10 ml per feed until the child is satisfied (Ashworth et al., 2003:18; WHO, 2013b:40). The WHO recommend monitoring for indications of heart failure by observing the pulse and heart rate as follows: If there is an increase in pulse by 25 beats per minute and the rate of breathing increases by five breaths per minute and these readings continue for two consecutive four-hourly measurements, then the feed volume needs to be decreased to 100 ml/kg for the next 24 hours. On the second day, the volume can be increased to 115 ml/kg. On the third and fourth day, the feed can be increased to 130 ml/kg, followed by the standard rehabilitation guidelines (Ashworth et al., 2003:18-19; WHO, 2013a:214-215). Lastly, the rehabilitation phase, where large amounts of energy and protein are provided, aims to regain lost weight rapidly (Ashworth et al., 2003:18; WHO, 2013b:40).

The WHO dietary requirements for SAM (6 – 59 months) during the different phases (Ashworth et al., 2003:17,19; WHO, 2013b:44) are summarised as follows:

- Initial stabilisation phase
  - Energy: 100 kcal/kg/day (75 kcal/kg in severe oedema based on volume of recommended F-75)
  - Protein: 1 – 1.5 g/kg/day (0.9 g/kg in severe oedema based on recommended volume of F-75)
  - Encourage breastfeeding, but give prescribed amounts of F-75 formula.
- Transition phase (two to three days after initial stabilisation)
  - Energy: 100 – 135 kcal/kg

  - Protein: not specified
- Rehabilitation phase
  - Energy: 150-220 kcal/kg/d
  - Protein: 4-6 g protein/kg/d
  - Encourage continued breastfeeding if breastfeeding.

Feeding recommendations by the WHO for infants less than six months are summarised as follows (WHO, 2013a:216; WHO, 2013b:64):

- Breastfeeding should be prioritised (WHO, 2013b:64).
- A supplementary feed should also be given as follows:
  - Infants with severe wasting without oedema should be given expressed breast milk or infant formula / F-75 / diluted F-100 if expressed breastmilk is not available.
  - Infants with oedema should be given infant formula / F-75 supplementary to breast milk.
  - Undiluted F-100 should not be prescribed at any stage of dietary treatment.
  - If breastfeeding is not possible, patients should be given commercial infant formula.

In 2005, South African adopted the WHO 10-steps to treat SAM in children under five years (Biggs, 2013:175). In a local study investigating how dietitians manage SAM in a clinical setting with a high prevalence of HIV, Biggs (2013:175,179) found that dietitians in KwaZulu-Natal followed their own expert opinion rather than the WHO protocol, and preferred to use commercial formula rather than F-75 and F-100. Concerns that were cited related to bacterial contamination and lactose content as malnourished patients often present with lactose intolerance due to flattening of the intestinal villi. The study further identified a lack of clinical experience in the public sector which necessitates the development of more specific protocols for the treatment of SAM that can be adapted to local circumstances to comprehensively address the impact of HIV on SAM (Biggs, 2013:175,178-179).

To conclude, applying the WHO guidelines has been successful in improving outcomes in children with SAM (Tickell & Denno, 2016:648). However, Tickell & Denno, (2016:648) argue that the treatment guidelines for SAM were developed

mainly based on expert opinion rather than scientific evidence and believe that the guidelines could be improved with more research.

2.3 Refeeding syndrome

Refeeding syndrome has been described since the 1940s and is still not entirely understood (Friedli et al., 2017:156). It usually develops when diets, especially those low in phosphorous and magnesium and high in carbohydrates are introduced after periods of starvation (Hother et al., 2016:2).

2.3.1 Definition of refeeding syndrome: an overview of problematic considerations

Friedli et al. (2020b:137) summarise the hallmarks of RFS as “electrolyte shifts (hypophosphataemia, hypokalaemia and hypomagnesaemia) and vitamin deficiency (thiamine), with or without clinical symptoms (peripheral oedema, tachycardia and tachypnoea)”. While there is some consensus that the main characteristics of RFS are hypophosphataemia and the development of the syndrome within five days after initiating feeding, no agreement has been reached on a standardised definition of RFS (Friedli et al., 2017:151; Friedli et al., 2020b:136; da Silva et al., 2020:178). Already in 1990, Solomon and Kirby proposed that the definition and components of RFS include “the metabolic and physiologic consequences of the depletion, repletion, compartmental shifts and interrelationships of phosphorous, potassium, magnesium, glucose metabolism, vitamin deficiency and fluid resuscitation” (Solomon & Kirby, 1990:91). Friedli et al., (2017:155-158), after conducting a systematic review on the topic, noted that almost thirty years later, there is still no agreement on whether the definition should only include electrolyte disturbances, or whether it should be broadened to include clinical features. In addition, Crook (2014:1454) suggested that RFS might be more accurately described as refeeding hypophosphataemia as the presence of symptoms should define RFS. Furthermore, Skipper (2012:34) argued that RFS is not consistent with its presentation concerning biochemical and clinical abnormalities and that there can be many other reasons for the development of hypophosphataemia, which could imply that electrolyte disturbances in malnourished cases might reflect normal physiological responses to underfeeding (Crook, 2014:1449; Friedli et al., 2017:159). In recent literature, two consensus

recommendations for the diagnosis of RFS have been published. Firstly, Friedli et al. (2020b:139-140) differentiates between manifest RFS and imminent RFS. Manifest RFS is defined by electrolyte imbalances accompanied by clinical symptoms such as heart failure, respiratory insufficiency and peripheral oedema, whereas imminent RFS is defined by the presence of electrolyte imbalances only. Secondly, da Silva et al. (2020:190) proposed the following definition: "A decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10%–20% (mild RFS), 20%–30% (moderate RFS), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamine deficiency (severe RFS); and occurring within five days of reinitiating or substantially increasing energy provision".

Adding to the discussion, another consideration when defining RFS is that there is no consensus on the exact cut-off points that define hypophosphataemia. The systematic review by Friedli et al. (2017) which encompassed 45 studies including 6608 patients, indicated that ranges used in previous studies varied between blood phosphate levels "<1 mmol/L and below the normal range, to <0.32 mmol/L, or decreased rate from baseline >30% or >0.16 mmol/L" (Friedli et al., 2017:153). They found that the most frequently used definitions were those noted in the studies of Marik & Bedigian (1996) and Rio et al. (2013), summarised in Table 2.3. (Friedli et al., 2017:153).

Table 2.3: Most frequently used definitions of refeeding syndrome (Friedli et al., 2017:154-155)

Author	Definition of RFS
Marik & Bedigian (1996:1044)	A drop in blood PO_4 levels by >0.16 mmol/L to <0.65 mmol/L, accompanied by possible other electrolyte disturbances
Rio et al. (2013:2)	Blood electrolyte disturbances (K levels <2.5 mmol/L, PO_4 levels <0.32 mmol/L, Mg levels <0.5 mmol/L) and clinical symptoms (peripheral oedema or acute circulatory fluid overload) and disturbance to organ function (respiratory failure, cardiac failure, or pulmonary oedema)

The degree of hypophosphataemia has also been classified according to the severity of symptoms, as moderate (1.5 – 2.2 mg/dL (0.5 – 0.7 mmol/L) and severe (<1.5 mg/dL (0.5 mmol/dL) (Parli et al., 2014:197). Other biochemical abnormalities that are likely to be present in RFS and lead to complications are similarly classified as moderate (2.5-3.5 mEq/L / 2.5 – 3mmol/L) to severe (<2.5 mEq/L / <2.5 mmol/L) hypokalaemia, and moderate (<1.5 mg/dL / <0.616 mmol/L) to severe (<1.0 mg/dL /

<0.411 mmol/L) hypomagnesaemia (Parli et al., 2014:197-199; Skipper, 2012:35; Tresley & Sheean, 2008:2105).

2.3.2 Risk factors for developing refeeding syndrome

To prevent RFS, it is vital to identify risk factors for developing RFS (Parli et al., 2014:201). Table 2.4 summarises the risk factors identified in the National Collaborating Centre for Acute Care (NICE) guidelines (National Institute for Health and Care Excellence). Notably, Friedli et al. (2017:157), reported that most of the 45 studies included in their 2017 systematic review, found that the risk factors for developing RFS published by the National Collaborating Centre for Acute in 2006, were associated with the development of RFS. Additional risk factors for RFS, identified in the systematic review, were enteral feeding, age and higher malnutrition risk scores (i.e. nutritional risk screening (NRS 2002) score ≥3 points) (Friedli et al., 2017:157-158).

Table 2.4: Criteria for determining people at high risk of developing refeeding problems (NICE, 2006:40)

A patient has one or more of the following:
▪ BMI < 16 kg/m^2 ▪ Unintentional weight loss >5% within the last three to six months ▪ Little or no nutritional intake for more than ten days ▪ Low levels of potassium, phosphate or magnesium prior to feeding
A patient has two or more of the following:
▪ BMI < 18.5 kg/m^2 ▪ Unintentional weight loss greater than 10% within the last three to six months ▪ little or no nutritional intake for more than five days ▪ A history of alcohol abuse or drugs including insulin, chemotherapy, antacids or diuretics.

Furthermore, in a paediatric context, Table 2.5 indicates the risk factors recommended by ASPEN for developing RFS in children. The criteria listed in this table are not considered comprehensive, and the impact of the presence of one or more of the characteristics cannot be determined owing to the incidence not being known. Children have important differences when compared to adults. Generally, the risk of RFS is often linked to the degree of malnutrition, especially in non-DRM. Adults seem to be able to handle a longer period of starvation compared to children. Insufficient intake of food over a short period of time can be more detrimental in children, as they have increased metabolic needs for growth, compared to adults. For these reasons,

the risk criteria for children were stratified according to mild, moderate and severe risk based on various anthropometry cut-offs, energy intake, degree of electrolyte abnormalities on admission, presence of co-morbidities and loss of muscle mass (da Silva et al., 2020:190).

Table 2.5: ASPEN consensus criteria[1] for identifying paediatric patients at risk for refeeding syndrome (da Silva et al., 2020:189)

	Mild risk: 3 risk categories needed	Moderate risk: 2 risk criteria needed	Significant risk: 1 risk criteria needed
Weight-for-length Z-score (1 – 24 months) or BMI[2]-for-age Z-score (2 – 20 years)	−1 to −1.9 Z-score that is a change from baseline	−2 to −2.9 Z-score that is a change from baseline	−3 Z-score or greater that is a change from baseline
Weight loss	<75% of norm for expected weight gain	<50% of norm for expected weight gain	<25% of norm for expected weight gain
Energy intake	3 – 5 consecutive days of protein or energy intake <75% of estimated need	5 – 7 consecutive days of protein or energy intake <75% of estimated need	>7 consecutive days of protein or energy intake <75% of estimated need
Abnormal prefeeding serum potassium, phosphorous, or magnesium concentrations[3]	Mildly abnormal or decreased to 25% below lower limit of normal	Moderately/significantly abnormal or down to 25% - 50% below lower of normal	Moderately/significantly abnormal or down to 25% - 50% below lower of normal
Higher-risk co-morbidities	Mild disease	Moderate disease	Severe disease
Loss of subcutaneous fat	Evidence of mild loss **OR** Mid-upper arm circumference Z-score of –1 to –1.9 Z-score	Evidence of moderate loss **OR** Mid-upper arm circumference Z-score of –2 to –2.9 Z-score Evidence of mild or moderate loss **OR** Mid-upper arm circumference Z-score of –2 to –2.9	Evidence of severe loss **OR** Mid-upper arm circumference Z-score of –1 to –1.9 Z-score Evidence of severe or moderate loss **OR** Mid-upper arm circumference Z-score of –3 or greater

[1] Not intended for use in patients at ≤28 days of life or ≤44 weeks' corrected gestational age.
[2] Body mass index
[3] Electrolytes may be normal despite total-body deficiency, which is believed to increase risk of refeeding syndrome.

2.3.3 Pathophysiology of starvation and refeeding syndrome

Friedli et al. (2020b:137) state that at the time of a systematic review in 2017, the pathophysiology of RFS was not yet entirely understood. However, mechanisms that have been identified that explain the development of RFS include the pathophysiology of starvation followed by the reintroduction of nutrients, particularly through diets high in carbohydrate (Friedli et al., 2017:152; WHO, 2013b:41).

During starvation, insulin production decrease, and levels of glucagon increase following a reduced intake of carbohydrates (Ormerod et al., 2010:686). The body's metabolism, therefore, shifts from anabolism to catabolism rapidly converting glycogen stores into glucose and adjusting from using carbohydrates for energy to using protein, and fat for energy through the process of gluconeogenesis (Ormerod et al., 2010:686). In this process fatty acids, glycerol and amino acids are released from adipose tissue and muscles, respectively. Free fatty acids and amino acids are, therefore, used as a significant energy source to replace glucose. The catabolism of fat tissue and muscles leads to loss of muscle mass (Crook et al., 2001:632-633). During prolonged fasting, the body undergoes hormonal and metabolic changes, and the liver eventually slows down the rate of gluconeogenesis to prevent the breakdown of protein and muscle, aimed at preserving muscle protein. During this protein sparing phase of starvation, fat is broken down into fatty acids and ketone bodies to provide energy through the process of lipolysis and ketogenesis (Grover & Ee, 2009:1060). Then, muscle and other tissues use fatty acids instead of ketone bodies as the primary source of energy. Therefore, ketone bodies in the blood increase, which stimulates the brain to use ketone bodies instead of glucose as its primary source of energy (Mehanna et al., 2008:1496). During these metabolic adaptations to starvation, intracellular vitamin and electrolyte stores, including thiamine, phosphate, magnesium and potassium stores become depleted. However, levels of these electrolytes in the blood may remain at normal levels due to contraction of the intracellular compartment that contains these minerals, as well as decreased renal excretion thereof (Mehanna et al., 2008:1496; Ormerod et al., 2010:686). Therefore, malnourished patients who present with normal blood electrolyte levels, are not necessarily at lower risk of developing RFS after feeding is initiated (Ormerod et al., 2010:686:).

Stanga et al. (2008:687) state that patients who are severely malnourished, are particularly at risk of developing RFS. Studies have shown that RFS develops after reintroducing feeds, particularly carbohydrates, too rapidly in malnourished patients. (Afzal et al., 2002:517; Hother et al., 2016:2; Stanga et al., 2008:687; Tresley & Sheean, 2008:2105). Reintroducing nutrients in a starved and catabolic patient, causes a sudden rise of glucose concentration and insulin secretion due to the shift of energy metabolism from catabolism to anabolism, thus from fat to carbohydrate metabolism (Crook et al., 2001:633; Friedli et al., 2017:152; Namusoke et al.,

2016:551). The surge of insulin secretion causes the rapid movement of glucose, water and electrolytes, notably phosphate, magnesium and potassium, from the extracellular compartment into the cells, and increases protein and glycogen synthesis. As a result, thiamine is rapidly depleted as it is a cofactor in glycolysis (Crook et al., 2001:633; Namusoke et al., 2016:551; Stanga et al., 2008:688). This drastic shift in electrolytes leads to reduced excretion of water and sodium, expanding the extracellular volume resulting in fluid overload and an increased risk of peripheral and pulmonary oedema and heart failure due to cardiac decompensation (Friedli et al., 2017; Tresley & Sheean, 2008:2105). The transcellular shift and relocation of electrolytes result in hypophosphataemia, hypokalaemia, and hypomagnesaemia, which can cause lethal complications such as cardiac arrhythmias or spasm (Friedli et al., 2017:152; Tresley & Sheean, 2008:2105). Thiamine deficiency can cause Wernicke's encephalopathy and/or cardiomyopathy (Stanga et al., 2008:688). Also, hypophosphataemia disturbs the production of phosphate-dependent adenosine triphosphate, which can lead to rhabdomyolysis, muscle weakness, and impaired hematopoiesis resulting in anaemia and oxygen supply reduction. Figure 2.4 provides a visual representation of the pathogenesis and features of RFS.

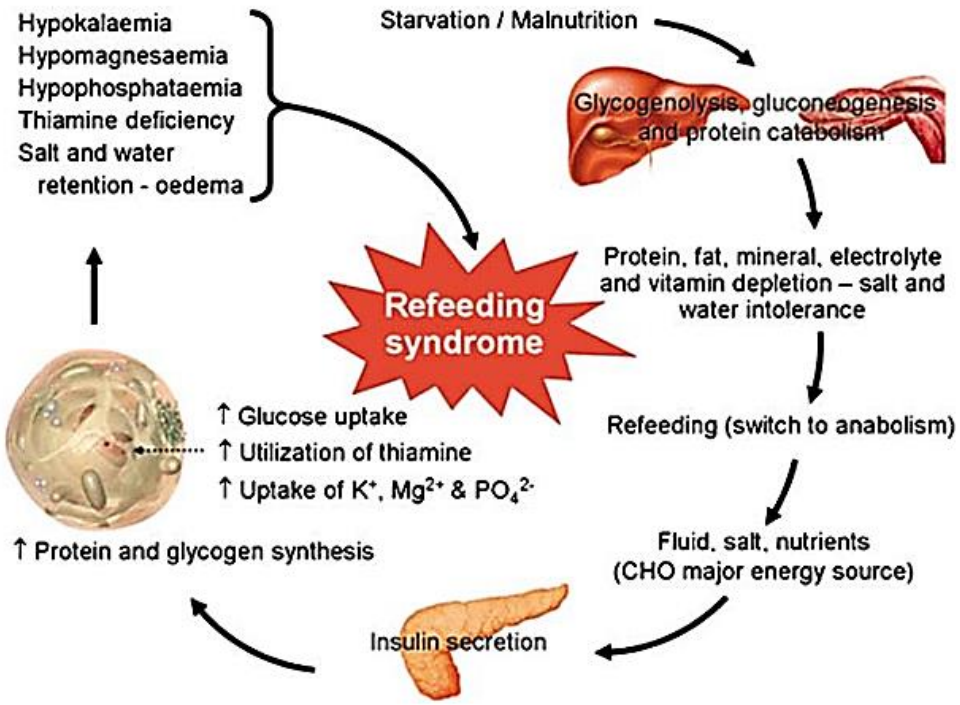


Figure 2.5: Pathogenesis and features of the refeeding syndrome (Stanga et al.,2008:688)

2.3.4 Incidence of refeeding syndrome in children

In their 2017 systematic review, Friedli et al. (2020b:137) found that the overall reported incidence rates of RFS were heterogeneous, ranging from very low up to 48%. In children, the incidence of RFS is not yet known due to a lack of research, (Mbethe & Mda, 2017:2). A systematic review of the literature from 1966 to 2001, by Afzal et al. (2002:515), found reports of only 27 cases of children in the world diagnosed with RFS, defined in this review as a drop in serum phosphate levels, after having received oral/enteral feeding (Table 2.6). Severe acute malnutrition was the underlying diagnosis in only 14 of these cases (Afzal et al., 2002:516-517). Since Afzal et al.'s publication, a limited number of studies have reported on the prevalence of RFS in acutely malnourished children.

Table 2.6: Cases of refeeding syndrome reported with enteral nutrition in children (Afzal et al., 2002:517)

Author	Year	No. of patients	Age range	Underlying diagnosis	Clinical features	Deaths
Patrick et al.	1977	6	11 – 28 months	Kwashiorkor	Cardiac arrest	4
Mezoff et al.	1989	5	6 months – 19 years	Not recorded	Not recorded	0
Kaysar et al.	1991	1	16 years	Anorexia nervosa	Low phosphate only	0
Beumont et al.	1992	1	16 years	Anorexia nervosa	Delirium	0
Kohn et al.	1998	2	12 – 13 years	Anorexia nervosa	Cardiac arrest Delirium on day 7	0
Worley et al.	1998	3	3 – 12 years	Neurological disease Child neglect	Haemolysis, rhabdomyolysis Low phosphate only	0
Manary et al.	1998	8	<10 years	Kwashiorkor	Phosphates <0.32 mmol/L	5
Fisher et al.	2000	1	16 years	Anorexia nervosa	Hypotension and bradycardia	0
Total		**27**	**6 months – 19 years**			**9**

Moreover, studies have reported on the phosphate and other electrolyte levels on admission, and changes after admission, without referring to the onset of feeding or making an overt diagnosis of RFS. A possible reason for this may have been due to the lack of a standardised definition for RFS (Friedli et al., 2017:158). A study in Bangladesh in 2013, which included 48 children with SAM and 56 children without SAM, identified that 43.8% of children with SAM had a phosphate value that was significantly lower on day two and day four of hospitalisation compared to phosphate levels on admission (Yoshimatsu et al., 2013:79). This study also determined that hypophosphataemia was more common in children with SAM who had sepsis.

Furthermore, potassium <2.5 mmol/L and a MUAC <11.5 cm on admission were identified as risk factors for the development of moderate to severe hypophosphataemia in children with sepsis (Yoshimatsu et al., 2013:83). A study in Uganda showed that 79% of children with SAM presented with hypophosphataemia on admission, with no incidence of severe hypophosphataemia (Namusoke et al., 2016:551). Furthermore, a study performed in Cameroon, where RFS is underdiagnosed, which included 42 children with SAM aimed at describing the different electrolyte abnormalities that occur during the first phase of treatment by measuring potassium, magnesium and phosphorus on admission and on day two of hospitalisation (Pangetna et al., 2019:S638). The following results were found: On day two of hospitalisation, 59.3% of children presented with hypophosphataemia, 21.4% presented with hypokalaemia and 3.12% presented with hypomagnesaemia. Notably, 25% of the children presented both with hypophosphataemia and hypokalaemia on day two of hospitalisation, and 3.12% of the children presented both with hypophosphataemia and hypomagnesaemia on day two of admission (Pangetna et al., 2019:S638).

An in-depth search of all the major databases of peer-reviewed studies found only two studies (both relatively recent) that explicitly reported on the incidence of RFS in children treated for SAM. Firstly, a study at Kenyatta National Hospital in Kenya reported a 21% incidence of RFS among 161 children admitted with SAM. In this study, electrolytes were measured 48 hours after feeding was initiated, and RFS was diagnosed if either potassium or phosphorus dropped >0.3 mmol/L from baseline. It is worth noting that the occurrence of RFS was significantly associated with HIV infection (Kerubo, 2018:69). Secondly, a study including 104 participants with SAM (33% HIV positive) admitted to a hospital in Pretoria, South Africa in 2014/2015, reported that the incidence of RFS was 15% (Mbethe & Mda, 2017:1) based on a phosphate blood value <1 mmol/L on day five of hospitalisation.(Mbethe & Mda, 2017:5)

2.3.5 Nutritional management of refeeding syndrome

According to Wagstaff (2011:511), dietetic practices in the management of RFS are inconsistent. To complicate matters, different sets of dietary guidelines have been developed, independent of each other, for the treatment of SAM and RFS.

For adults, different sets of guidelines have been published: Firstly, the European NICE guidelines recommend that nutrition support should be initiated at ≤ 50% of total energy and protein requirements (NICE, 2006:82. Secondly, Stanga et al. (2008:692) recommend starting energy requirements at 42 kJ/kg/day (10 kcal/kg/day) and slowly increasing to 63 kJ/kg/day (15 kcal/kg/day). Additionally, macronutrients should contribute 50 – 60% of total energy as carbohydrates, 30 – 40% as fat, and as 15 – 20% protein (Stanga et al., 2008:692). Thirdly, Tresley & Sheean (2008:2107) recommend refeeding at 20 kcal/kg/day or about 50% of total energy requirements and limiting protein to 1.0 – 1.5 g/kg/day. Lastly, two sets of recommendations were published in 2020. Firstly, the American Society for Parenteral and Enteral Nutrition (ASPEN) has recommended initiating feeds at 10 – 20 kcal/kg for the first day and increasing by 33% of the total goal every one to two days (da Silva et al., 2020:13). Secondly, a summary of the nutritional requirements for preventing RFS published by Friedli et al. (2020b:138) is indicated in Table 2.7.

Table 2.7: Prevention of refeeding syndrome during nutritional therapy
(Friedli et al., 2020b:138)

<table>
<tr><th colspan="5">Energy, protein, carbohydrates and fat requirements for the prevention of RFS</th></tr>
<tr><td>Risk stratification for RFS</td><td>No risk</td><td>Low risk
1 minor risk factor</td><td>High risk
1 major or 2 minor risk factors</td><td>Very high risk
BMI<14; weight loss >20%; starvation >15 days</td></tr>
<tr><td>Day 1 – 3</td><td rowspan="7">Energy (by all routes): full requirements (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td>Energy (by all routes): 15 – 25 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td>Energy (by all routes): 10 – 15 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td>Energy (by all routes): 15 – 25 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td></tr>
<tr><td>Day 4</td><td>Energy (by all routes): 30 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td>Energy (by all routes): 15 – 25 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td rowspan="3">Energy (by all routes): 10 – 20 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td></tr>
<tr><td>Day 5</td><td rowspan="3">Energy (by all routes): full requirements (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td rowspan="2">Energy (by all routes): 30 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td></tr>
<tr><td>Day 6</td></tr>
<tr><td>Days 7 – 9</td><td rowspan="2">Energy (by all routes): full requirements (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td><td>Energy (by all routes): 20 – 30 kcal/kg/d (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td></tr>
<tr><td>>10 days</td><td>Energy (by all routes): full requirements (40 – 60% carbohydrates, 30 – 40% fat, 15 – 20% protein)</td></tr>
</table>

In the context of paediatrics, the following recommendations for the prevention of RFS in children have been identified in the literature. Firstly, a set of guidelines, developed by Afzal et al. (2002:518) and endorsed by Braegger et al., (2010:117) for the prevention of RFS in severe cases of malnutrition that recommend initiating energy requirements at 75% of the total requirements namely:

- <7 years old: 80–100 kcal/kg/day;
- 7–10 years old: 75 kcal/kg/day;
- 11–14 years old: 60 kcal/kg/day;
- 15–18 years old: 50 kcal/kg/day; and
- Initiating protein at 0.6 – 1.0 g/kg/day and gradually increasing to 1.2 - 1.5 g/kg/day. If feeding is tolerated, energy and protein can be gradually increased over three to five days (Afzal et al., 2002:518).

Secondly, O'Connor & Nicholls (2015:675) specify that carbohydrates should not exceed 60% of total energy and recommend different feeding phases as indicated in Table 2.8, but does not specify age groups. Thirdly, Figure 2.6 indicates an algorithm for the management of RFS in paediatric ICU patients (Meyer & Marino, 2015:78). Lastly, ASPEN released consensus guidelines in 2020 for the prevention and management of RFS in paediatric patients who are likely to develop RFS. The section on dietary management in these patients is indicated in Table 2.9.

Table 2.8: Refeeding phases in high-risk paediatric patients (O'Connor & Nicholls, 2015:675)

Refeeding phase	Target energy requirements and weight gain
Primary Days 1 – 2	▪ Commence at 40 kcal (167 kJ)/kg/day ▪ Increase 200 kcal (840 kJ)/day until secondary refeeding phase reached ▪ Correct deranged electrolytes; do not stop refeeding ▪ Weight loss/maintenance likely during this primary refeeding phase ▪ Consider oral thiamine 100 – 200 mg twice a day, continue for 10 days
Secondary Days 2 – 4	▪ Basal metabolic rate (BMR) x physical activity level (PAL) ▪ Maintain secondary refeeding phase if adequate weight gain (0.5 – 1.0 kg/ week) ▪ Once weight gain reduces, increase 200 – 300 kcal (840 – 1255 kJ)/day until tertiary refeeding phase reached
Tertiary Days 7 – 14	▪ Estimated average requirement (EAR) energy for height age ▪ Maintain tertiary phase if adequate weight gain (0.5 – 1.0 kg/ week)
Progression	▪ If sufficient weight gain not achieved with EAR continue to increase energy intake 200 – 300 kcal (840 – 1255 kJ) every 4 days until weight increase of 0.5 – 1 kg/week
Maintenance	▪ Once the weight is >85% median BMI, weight gain can be slowed or maintained depending upon the therapeutic plan as discussed with the multidisciplinary team

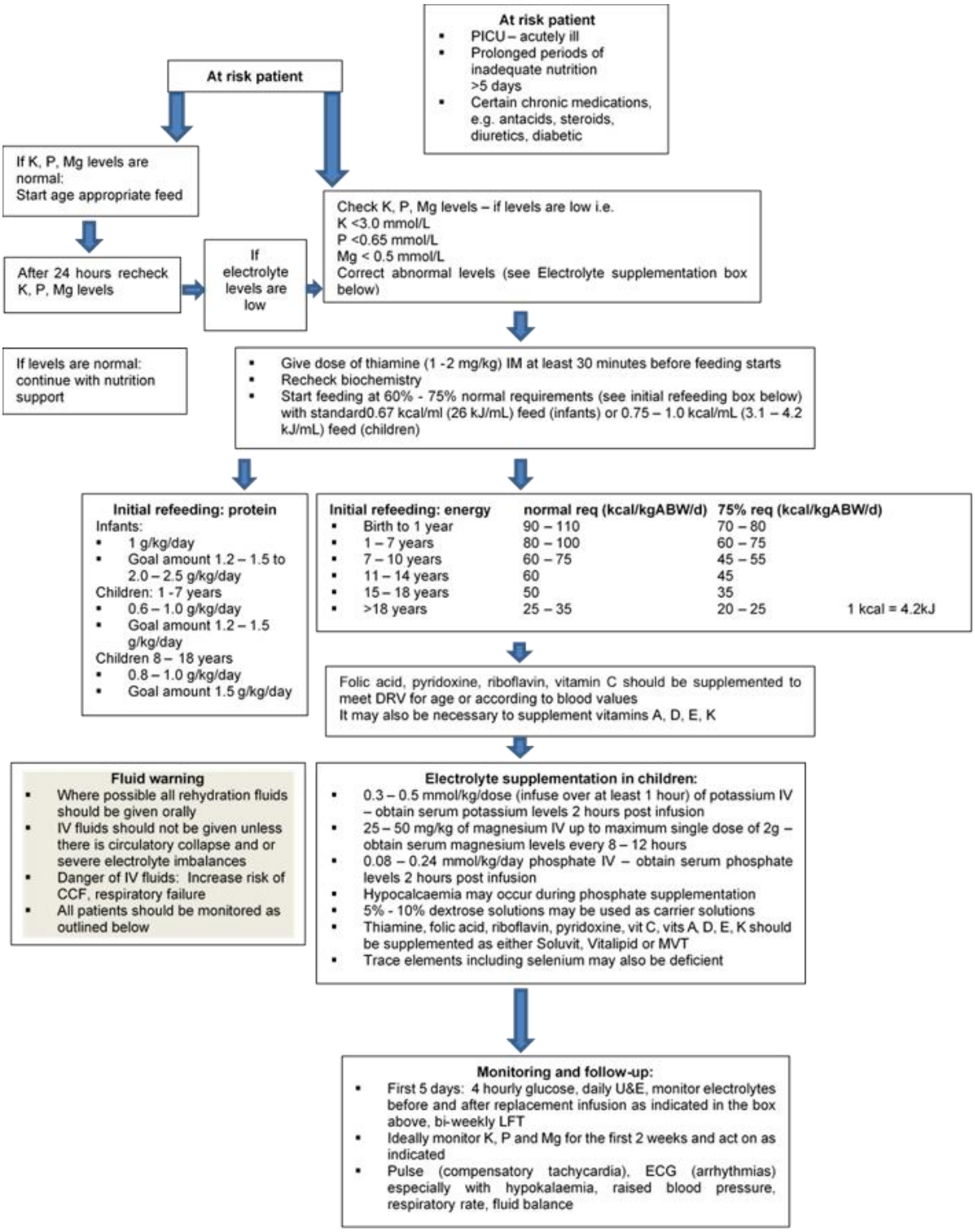


Figure 2.6: Management of refeeding syndrome in the paediatric intensive care unit (Meyer & Marino, 2015:78)

Table 2.9: ASPEN consensus recommendations for avoidance and treatment of RFS in at-risk paediatric patients (da Silva et al., 2020)

Aspect of care	Recommendations
Initiation of nutrition	Initiate nutrition at a maximum of 40%–50% goal, but usually starting the glucose infusion rate around 4–6 mg/kg/min and advancing by 1–2 mg/kg/min daily as blood glucose levels allow until you reach a max of 14–18 mg/kg/min. This includes enteral as well as parenteral glucose. Calories from IV dextrose solutions and medications being infused in dextrose should be considered in the limits above and/or initiated with caution in patients at moderate to severe risk for RS. If the patient is already receiving IV dextrose for several days and/or medications in dextrose and has been asymptomatic with stable electrolytes, calories from nutrition may be reintroduced at a higher amount
Fluid restriction	No recommendation
Protein restriction	No recommendation

In order to identify electrolyte imbalances and make a diagnosis, biochemistry should be measured every day in the first week and three times or more in the following week (Mehanna et al., 2008:1498). If RFS is diagnosed, the rate of feeding should be decreased and low serum electrolytes need to be replaced (Mehanna et al., 2008:336).

2.4 Refeeding syndrome in severe acute malnutrition

In the 1980s and 1990s, RFS and diarrhoea occurred as a result of introducing large volumes of F-100. This led to the implementation of transition phase feeding protocols in malnutrition centres, which had successful outcomes. The transition phase of feeding was, therefore, adopted by the WHO as an intermediate phase of feeding between the stabilisation and rehabilitation phase of feeding. (WHO, 2013b:40). However, according to Namusoke et al. (2016:551), there is a lack of research on the effect of feeding on phosphate in the transition phase as research has mainly focused on the early days of dietary treatment. Furthermore, concerning electrolyte supplementation, Brewster (2011:97) has recommended that phosphate supplementation should be added to the WHO protocol to prevent RFS.

Overall, it seems that the WHO feeding guidelines for the treatment of SAM improve patients' outcomes and are effective in reducing the risk of RFS by slowly increasing

energy when transitioning from the stabilisation to the rehabilitation phase, but it remains unclear whether this approach can be improved (WHO, 2013b:40-41).

2.5 Summary

Severe acute malnutrition remains a problem worldwide as it contributes to significant mortality in children below five years. Furthermore, children diagnosed with SAM are at an increased risk of developing RFS, which if left unrecognised and untreated, could lead to death and, therefore, further increase mortality rates in children with SAM.

To date, guidelines to treat SAM, and guidelines to prevent and treat RFS have been developing separately. Thus, despite RFS being directly linked to malnutrition, the dietary guidelines are inconsistent, leading to many researchers expressing the need for more studies in children in both these fields. Also, a major complicating factor in reaching more insight into SAM-related RFS remains the lack of a uniform definition of RFS.

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CHAPTER 3: METHODOLOGY

3.1 Introduction

This study determined the incidence of RFS, characterised by hypophosphataemia, and associated factors related to refeeding in children aged 0 – 59 months diagnosed with SAM. In this chapter, methodology including ethical considerations, study design and sampling, study outline, measured variables and techniques, validity, reliability and avoiding possible measurement errors, data analysis methods and challenges encountered during the execution of the study, were recorded.

3.2 Ethical considerations

Ethical approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (Appendix B). Permission was also obtained from the Gauteng Department of Health / National Health Research Database as well as the Chief Executive Officer of Rahima Moosa Mother and Child Hospital (Appendix C), to perform the study and retrieve retrospective information from archived hospital files and NCRs from October 2014 until December 2018. The personal data of all patients, as well as information of physicians and other medical professionals, were kept confidential.

3.3 Study design and sampling

The following study design and sampling methods were applied.

3.3.1 Study design

A retrospective analytical cohort study of retrievable hospital files and NCRs was conducted. The reasons for not choosing a more rigorous prospective study design, were as follows:

i. Firstly, it was the researcher's experience working at the Rahima Moosa Mother and Child Hospital that children in the eligible age group that were admitted, were often not accompanied by a legal guardian but instead by a relative or acquaintance of the legal guardian. This posed an ethical dilemma in getting the necessary informed consent to include a child in the study. The concern was that this might have limited the number of patients that were eligible for the study within the time frame for the completion of a Master's degree.

ii. Secondly, as the number of patients admitted with SAM, varied from month to month, finding sufficient participants within the time frame for the completion of a Master's degree was foreseen as a challenge.

iii. Lastly, a prospective study design was not deemed suitable because the study aimed to compare patients who developed RFS to those who did not, and this would have meant that the WHO feeding protocol would have had to be strictly adhered to for all participants. Thus, the researcher and other dietitians treating the patient would have been prevented from implementing an alternative nutritional management approach, based on their clinical judgement, if complications arose, for example, in patients with malabsorption, or renal or liver disease. This posed an ethical dilemma that the researcher chose to avoid.

3.3.2 Study population and sample selection

The study population included patients aged 0 – 59 months who had been admitted with SAM at the Rahima Moosa Mother and Child Hospital, Coronationville, Johannesburg, South Africa. At the time of the study, this was a regional academic 338-bed hospital comprised of gynaecological, anti-natal, high-care and paediatric sections. The paediatric sections comprised of the following wards (University of the Witwatersrand, 2017):

- Four general paediatric wards each with 20 – 30 beds (0 – 12 years);
- Two neonatal wards each with 35 beds;
- One Kangaroo Mother Care ward with 12 beds;
- One Neonatal Intensive Care with six beds; and
- One High Care unit with four beds.

The sample comprised of all patients aged 0 – 59 months, with retrievable archived hospital files, who had been admitted with SAM at this hospital. Finding the relevant files posed a challenge to sampling as, before 1 October 2014, the hospital only kept computerised statistics of the number of patients that had been admitted with SAM, without linking these to any patients' details or hospital numbers. Also, the hospital at that stage archived all hospital files only according to hospital number, with no link to diagnosis, thus making it impossible to trace the files of patients that would have been eligible for inclusion in the study. In October 2014, however, a checklist was implemented to audit the management of patients with SAM at the Rahima Moosa Mother and Child Hospital. When a patient was admitted with SAM, a blank checklist was placed in the hospital file. These SAM checklists had to be completed by the dietitian during hospitalisation or once the patient was discharged, and then was removed by the dietitian from the hospital file and filed at the Dietetics Department. The SAM checklist included the following information: name and surname, date of birth, hospital number, weight, height, MUAC, presence of oedema and an evaluation of the WHO 10-steps for the in-patient management of SAM. Because this information was held in the Department of Dietetics at the hospital, it afforded a way for the researcher to access the relevant hospital files for this study. Therefore, the sampling was finally restricted to children admitted with SAM from 1 October 2014 to 31 December 2018 (as data extraction commenced in early 2019) and an overview of the SAM statistics are summarised in Table 3.1.

Table 3.1: Overview of SAM statistics at Rahima Moosa Mother and Child Hospital

SAM Statistics for 1 October 2014 – 31 October 2018	n
Total number of patients admitted and diagnosed with SAM according to computerised statistics kept by the Dietetic Department at Rahima Moosa Mother and Child Hospital	592
Total number of hospital files retrieved	148

One limitation of having to rely on the SAM checklists to identify participants to include in the study was that not all checklists could be obtained because some patients were discharged before the checklists could be removed from the hospital files. Hence, the total number of patients admitted with SAM differed to the total number of checklists

filed at the Dietetics Department. Furthermore, after using the information from the checklists to retrieve hospital files from the hospital archives for the study, many hospital files had seemingly been misfiled and could, therefore, not be traced and obtained. Therefore, the study population (eligible patients that could be identified) did not fully represent the entire population of children that were admitted with SAM at the Rahima Moosa Mother and Child Hospital for the period under review. Finally, a total of 329 SAM checklists were identified, of which only 148 hospital files could be retrieved.

3.3.2.1 Inclusion criteria

Patients were eligible for inclusion in the study if they, according to their hospital files:

- Were admitted between 1 October 2014 and 31 December 2018;
- Were aged 0 – 59 months at the time of admission; and
- Were diagnosed with SAM that could be verified against the WHO Criteria.

Based on information from the SAM checklists, a clerk at the Hospital Archives Department retrieved the hospital files. The researcher then verified the diagnosis of SAM from information in each hospital file obtained. For this, the patient profile and anthropometry were recorded on a data sheet (Appendix D). The WHO criteria for the definition of SAM according to age and gender were applied. Thus, SAM was confirmed as follows (WHO, 2013:63):

- Patients aged below six months if:
  - ❖ Weight-for-length < -3 SD; and/or
  - ❖ Bilateral pitting oedema was present.
- Patients aged six months to five years using the criteria summarised in Table 3.2.

Table 3.2: Diagnostic criteria for SAM in children aged 6 - 59 months (WHO & UNICEF, 2009:2)

Indicator	Indices	Cut-off
Severe wasting (2)	Weight-for-length/height (1)	<-3 SD
Severe wasting (2)	MUAC	<11.5 cm
Bilateral oedema (3)	Clinical sign	Present

[1] Based on WHO Standards (www.who.int/child growth/standards) (WHO, 2016)
[2,3] Independent indicators of SAM that require urgent action

Only those patients for which the diagnosis of SAM could be confirmed were included in the study. The total number of eligible patients included as participants in the study was 126. Furthermore, dietitians could then retrieve the eligible participants NCRs which were filed at the Dietetics Department alphabetically, and according to which dietitian managed the patient when they were admitted. NCRs are dietetic records of patient management and include information on the dietary prescription.

3.3.2.2 Exclusion criteria

Patients who did not meet the criteria for SAM, despite having been diagnosed with SAM according to the SAM checklists and hospital files, were excluded from the study. The number of records excluded from the study was 26.

3.4 Steps to complete the study

Step 1: Obtained ethical approval from the Health Sciences Research Ethics Committee at the University of the Free State (Appendix B), as well as permission from Gauteng Department of Health and the Chief Executive Officer at Rahima Moosa Mother and Child Hospital (Appendix C);

Step 2: Retrieved hospital files from the Hospital Archives Department and NCRs from the Dietetics Department at Rahima Moosa Mother and Child Hospital;

Step 3: Applied the inclusion and exclusion criteria to identify the sample;

Step 4: Conducted a pilot study and made adjustments to the protocol and datasheets, based on the feedback from the pilot study;

Step 5: Obtained ethical approval from the Health Sciences Research Ethics Committee at the University of the Free State for the amendments to the protocol (Appendix E);

Step 6: Extracted and recorded the identified variables (see 3.5.2) onto a datasheet (Appendix D);

Step 7: Performed statistical analysis with the assistance of the Department of Biostatistics at the University of the Free State; and

Step 8: Interpreted the results and completed the dissertation.

3.5 Measurements

To support some of the variables chosen for this study, it is important to first explain the standard practice for patients, aged 0 – 59 months admitted to Rahima Moosa Mother and Child Hospital with SAM, at the time of the study.

3.5.1 Standard practice followed at the hospital for patients with SAM

On arrival at the hospital, the patient was weighed on a calibrated baby scale, length was measured using a length mat or height measured against a measuring poster on the wall, or with a stadiometer. MUAC was taken by the physician or nurse with a tape measure or a MUAC tape around the middle of the arm, vertical to the long axis at the level of the triceps skinfold site (Lee & Nieman, 2013:230). If the patient was diagnosed with SAM by the doctor according to the WHO criteria, F-75 was prescribed and administered on admission, according to the WHO guidelines (WHO, 2013a:209). Thereafter, the patients were referred to be assessed by the dietitian in the ward.

The dietitian normally re-measured the length/height, whilst weight was recorded daily by nursing staff using a calibrated baby scale. After the diagnosis of SAM was confirmed by the dietitian based on the WHO criteria, the dietitian then prescribed a commercial infant formula (standard, soy or extensively hydrolysed), which has a lower energy and higher protein content compared with F-75. In addition, the dietitian would prescribe modular supplements (e.g. sugar, sunflower oil, MCT oil, Duocal), which were mixed into the commercial infant formula, to meet the WHO energy requirements for the stabilisation phase of SAM. Patients also received the additional electrolyte and vitamins required as per the WHO protocol prescribed as medication by the doctor. The reason for using a commercial formula instead of F-75 after admission was that it was too expensive to provide ready-to-use F-75 for all patients diagnosed with SAM at that time. Thus, F-75 was reserved for use in the admission ward only at the time of the study. The assessment, management plan (including the calculation of feed prescribed), as well as follow-up assessments and management plans, were recorded in NCRs.

3.5.2 Variables and operational definitions

The following variables were recorded for all participants: socio-demographic and clinical profiles, SAM criteria, biochemistry, clinical signs /and medical complications and the dietary prescription.

3.5.2.1 Socio-demographic and clinical profiles

For the purpose of this study, the recorded participants' profiles included the date of birth, age, gender, country of origin, ethnicity, date of admission, date of discharge, date of death and length of hospital stay.

3.5.2.2 SAM criteria (anthropometry and presence of bilateral pitting oedema)

Anthropometrical indices and the presence of bilateral pitting oedema on which the diagnosis of SAM was based was verified according to the inclusion/exclusion criteria for the study, and were recorded for each participant based on the following:

i Weight-for-length/height

Weight-for-length/height is an indicator of growth used to identify wasting, or overweight and obesity in children between 0 – 59 months of age. According to WHO guidelines, weight-for-length/height < -3 SD is an independent criterion for the diagnosis of SAM (WHO/UNICEF, 2009:2). Weight and length/height was interpreted on the WHO Child Growth Indicator tables i.e. weight-for-length/height (Appendix F), and the interpretation was recorded on the datasheet.

ii Mid-upper arm circumference

Mid-upper arm circumference refers to “the circumference of the left upper arm measured at the mid-point between the tip of the shoulder and the tip of the elbow” (Saeed et al., 2015:26). According to the WHO guidelines, a MUAC of < 11.5 cm is an independent criterion for the diagnosis of SAM (WHO/UNICEF, 2009:2).

iii Bilateral pitting oedema

Oedematous malnutrition is an idiopathic condition and can be life-threatening (Rytter et al., 2015:1). Oedema is defined as “an accumulation of an excessive amount of watery fluid in cells, tissues, or serous cavities” (Stedman, 2008:484). When one applies pressure with one’s finger to oedema, and an indentation remains after the

pressure has been released, it is defined as pitting oedema (Stedman, 2008:1216). The pathophysiology of the formation of oedema in oedematous malnutrition remains unknown (Rytter et al., 2015:1; Bhutta et al., 2017:9). The presence of bilateral pitting oedema was used as an independent diagnostic factor for SAM as per the WHO (Ashworth et al., 2003:9).

3.5.2.3 Biochemistry

Biochemical values related to RFS were captured from the participants' hospital files from admission and through the first two weeks of hospitalisation. Blood levels of phosphate, potassium, magnesium, sodium, albumin, CRP, urea and creatinine (to assess renal function), liver enzymes (to assess liver function), INR, haemoglobin and platelets were recorded.

i Phosphate (and the definition of refeeding syndrome)

Phosphorous was used as the primary marker for RFS, as it has been described as the most common characteristic of RFS (Mehanna et al., 2008:1495; Parli et al., 2014:197; Araujo Castro & Vázquez Martínez, 2017; Rytter et al., 2017:494). For this study, hypophosphataemia was defined as values below the normal range based on the Royal College of Paediatrics and Child Health (RCPCH) reference ranges (RCPCH, 2016:3) (Appendix G). Furthermore, RFS was described as a drop in phosphate by more than 0.16mmol/L to a level below 0.65mmol/L, after initiation of nutritional support (Marik & Bedigian, 1996:1044; Afzal et al., 2002:518; Meyer & Marino, 2015:78; Olthof et al., 2018:1609).

ii Potassium

Hypokalaemia is likely to be present in RFS and leads to complications. The normal paediatric reference value for potassium in the blood is 3.5 to 5.5 mmol/L (RCPCH, 2016:3). For this study, moderate hypokalaemia was indicated by a potassium value of 2.5 – 3.5 mmol/L, and severe hypokalaemia by a value < 2.5 mmol/L (Tresley & Sheean, 2008:2105; Parli et al., 2014:197).

iii Magnesium

Hypomagnesaemia is also likely to be present in RFS and lead to complications (Parli et al., 2014:197). The normal paediatric reference value for magnesium in the blood

is 0.6 – 1.0 mmol/L and hypomagnesaemia was, therefore, indicated by levels below the normal range (RCPCH, 2016:3). Moderate to severe hypomagnesaemia was indicated by a value below 0.5 mmol/L (Meyer & Marino, 2015:78; Tresley & Sheean, 2008:2105).

iv Calcium

Mbethe & Mda, (2017:6) reported the presence of hypocalcaemia associated with RFS in children with SAM. For the purpose of this study, hypocalcaemia was indicated by calcium values below the RCPCH normal paediatric reference range for age, indicated in appendix G (RCPCH, 2016:3).

v Sodium

Hyponatraemia is one of the biochemical abnormalities that can manifest during RFS (Skipper, 2012:34). Hyponatraemia can occur during refeeding as a result of hyperglycaemia (Khan et al., 2011:2). When carbohydrates are rapidly introduced, the kidneys excrete less water and sodium resulting in fluid overload which can cause heart failure (Tresley & Sheean, 2008:2105; Araujo Castro & Vázquez Martínez, 2017:475). For this study, hyponatraemia was indicated by blood sodium values below the RCPCH normal paediatric reference range indicated in appendix G (RCPCH, 2016:3).

vi Albumin

Albumin is not a reliable indicator for nutritional status as it is influenced by underlying metabolic stress like inflammation and infections, but low levels predict morbidity and mortality (Kagansky et al., 2005:467; Marcason, 2017:1144). For this study, low blood albumin was defined as values below the RCPCH normal reference range for age, indicated in appendix G (RCPCH, 2016:4).

vii C-reactive protein

Elevated C-reactive protein has been associated with an increased risk of death in children with SAM (Rytter et al., 2017:500). According to the RCPCH normal paediatric reference values, elevated CRP is indicted by a value > 5 mg/L (RCPCH, 2016:7). For this study the values according to Rytter et al., (2017:497), were adhered

to; namely, a CRP concentration of >15 mg/L was noted as a biochemical risk factor for death in patients identified as SAM.

viii Renal function

Patients with RFS have an increased risk of renal abnormality; therefore, urea and creatinine were monitored to determine renal function abnormality (Afzal et al., 2002:518; Crook, 2014:1453). Elevated blood urea and creatinine were indicated by levels above the RCPCH normal paediatric reference range for age, indicated in appendix G (RCPCH, 2016:3).

ix Liver function tests

Liver dysfunction could be caused by RFS (Crook, 2014:1454). For the purpose of this study, abnormal levels of the following liver enzymes were considered as measures of liver dysfunction:

- Alanine aminotransferase (ALT);
- Total bilirubin (TBIL);
- Alkaline phosphatase (ALP); and
- Aspartate aminotransaminase (AST).

Of these, elevated ALT is the most significant indicator of acute and chronic liver damage, while TBIL, ALP and AST are also implicated (Stirnadel-Farrant et al., 2015:349). Deranged liver function was described as elevated levels of the above-mentioned liver enzymes according to the normal RCPCH reference ranges for age, indicated in appendix G (RCPCH, 2016:4-5).

x Haemoglobin

Haemoglobin levels are routinely used to identify anaemia (Hussain et al., 2014:1). Severe anaemia was identified as a cause of death in children aged 6 – 59 months admitted to SAM stabilisation centres in Southern Ethiopia (Gebremichael, 2015:4). . For this study, a haemoglobin level below 11 g/dL indicated anaemia (De Benoist & Mclean, 2008:4; Hussain et al., 2014:1) and a haemoglobin level below 7 g/dl indicated severe anaemia (WHO, 2011:3; Stevens et al., 2013:e17).

xi Platelet count

Low platelet count, also known as thrombocytopaenia, is associated with an increased risk of bleeding (Assinger & Shen, 2014:1). Emerging evidence has identified low platelet counts as “a surrogate marker for poor prognosis in septic patients” (Assinger & Shen, 2014:1). Furthermore, A study from South-West Ethiopia in 2010 showed that children with HIV infection with SAM were more at risk of death when their platelet count was less than 150 ($\times 10^3/\mu l$) (Tadesse et al., 2010:18). For this study, a platelet count of below 150 ($\times 10^3/\mu l$) was considered low (Assinger & Shen, 2014:2; RCPCH, 2016:1).

xii International normalised ratio

International normalised ratio is used to evaluate coagulation status and the risk of bleeding in a patient (Shikdar & Bhattacharya, 2019:1). De Maayer & Saloojee (2011: 3) found that an INR above 1.7 was a poor prognostic factor for death in children with severe malnutrition with oedema, and was, therefore, observed in this study.

3.5.2.4 Clinical signs and medical complications

Clinical signs and medical complications were recorded on day one of hospitalisation to determine whether there were common factors that present in children with SAM which may have played a role in developing RFS. If a significant clinical sign and/or medical complication were recorded as having appeared after admission, it was also recorded. The presence of the following clinical signs and medical complications that occurred on admission were recorded from hospital files:

i Acute gastroenteritis (diarrhoea with or without vomiting)

Acute gastroenteritis (AGE) is characterised by the sudden onset of diarrhoea with or without fever, stomach pain, nausea and vomiting. (Colletti et al., 2010:686). Dehydration, as a result of gastroenteritis, is a common occurrence in children with acute malnutrition (Mwangome et al., 2011:1). Dehydration secondary to diarrhoea was found to be the primary cause of death in children aged 6 – 59 months admitted to SAM stabilisation centres in Southern Ethiopia (Kumar et al., 2014:125; Gebremichael, 2015:4). In this study, the presence of vomiting, diarrhoea and AGE were recorded separately from hospital files.

ii Dehydration

Dehydration can be a result of fluid imbalances caused by RFS (Crook, 2014:1452). Moreover, dehydration secondary to diarrhoea is the leading cause of death in children with SAM (Gebremichael, 2015:4; Kumar et al., 2014:125). For these reasons, dehydration was an important medical complication to record.

iii Bilateral pitting oedema

Bilateral pitting oedema is an independent diagnostic clinical sign of SAM (WHO/UNICEF, 2009:2; WHO, 2013b:2). To add, severe bilateral pitting oedema in SAM has been associated with an increased risk of death (WHO, 2013b:23). Oedema has also been significantly associated with RFS (Mbethe & Mda, 2017:6). In addition, Rytter et al., (2017:499) found that hypophosphataemia in children with oedematous SAM was a risk factor for death. For these reasons, the presence of bilateral pitting oedema was also recorded from the hospital files.

iv Dermatosis

Dermatosis is a medical complication of SAM (Ashworth et al., 2003:35) and was, therefore, recorded from hospital files.

v Hypoglycaemia

Hypoglycaemia was found to be the fourth leading cause of death in children with SAM (Gebremichael, 2015:4) and was, therefore, recorded. Hypoglycaemia was defined as blood glucose below 3 mmol/L according to the WHO SAM guidelines (WHO, 2013a:201).

vi Hyperglycaemia

Hyperglycaemia is one of the metabolic manifestations of RFS and is attributed to the change from fat to carbohydrate metabolism after the abrupt introduction of carbohydrates after a period of starvation (Boateng et al., 2010:158; Boland et al., 2013:9). Normal blood glucose levels range between 4 – 7 mmol/L (Gilbert, 2009:1256). Hyperglycaemia was, therefore, classified as a glucose level above 7 mmol/L in this study (Patki & Chougule, 2014:8).

vii Hypothermia

Hypothermia has been identified as a cause of death in children with SAM (Gebremichael, 2015:4) and was, therefore, recorded.

viii Pneumonia

Pneumonia has been identified as the second leading cause of death in children with SAM in a Southern Ethiopian study (Gebremichael, 2015:4) and was, therefore, recorded.

ix Respiratory complications

The respiratory system is one of the many organ systems which can be affected by RFS (Boateng et al., 2010:156). In this study, respiratory system complications recorded encompassed one or more of the following: dyspnoea/respiratory distress, respiratory failure, ventilator dependence and diaphragm/intercostal muscle weakness (Boateng et al., 2010:157; Campbell, 2004:404). Furthermore, Kumar et al. (2014:125) found that acute respiratory tract infection was the second most common co-morbid disease in children aged 6 – 60 months admitted with SAM to Gandhi Memorial Hospital in India.

x Sepsis

Kumar et al. (2014:126), identified sepsis as a comorbidity in children admitted with SAM. Shock as a result of dehydration and sepsis in all likelihood co-exist in SAM (Ashworth et al., 2003:21). Therefore, the presence of sepsis was documented.

xi Septic shock

Septic shock has been identified as a medical complication associated with RFS in SAM (Mbethe & Mda, 2017:6) as well as a cause of death in children with SAM (Gebremichael, 2015:4) and was, therefore, documented.

xii Loss of appetite and nasogastric tube feeding

Nasogastric tube (NGT) feeding has been shown to increase the risk of RFS in certain clinical circumstances such as malnutrition (Afzal et al., 2002:515,516,519; Morton-Nance, 2013:20; Crook, 2014:1453; Bhutta et al., 2017:11). Children admitted with SAM with a low appetite i.e. children who consume less or equal to 80% of the prescribed feed, for two consecutive feeds, require NGT feeding (WHO, 2013a:209), which in turn increases the risk of RFS. For these reasons, NGT feeding was important to record.

xiii Hepatomegaly

Hepatomegaly is a complex characteristic typically seen in children with oedematous SAM (van Zutphen et al., 2016:1205,1206) and occurs due to fatty infiltration (Shashidhar & Grigsby, 2017:7). Plasma levels of free fatty acids increase during starvation as fat stores are mobilised to provide energy (WHO, 2004:34) which increase the movement of fatty acids from adipose tissue into the liver. Fat, therefore, accumulates in the liver because the increased influx of fatty acids is greater than the capacity of the liver to dispose of fat (Lewis et al., 1964:164,165,166) leading to hepatomegaly. Another cause of hepatomegaly, and a possible reason for the increased mortality associated with hepatomegaly in malnutrition, is the inability of the liver to sufficiently clear cellular debris, free radicals and toxins causing the accumulation of these products in the liver (Van Den Broeck, 1995:487). Liver dysfunction in malnutrition occurs due to physiological and metabolic changes known as reductive adaptations that take place during starvation to preserve energy and support life (WHO, 2004:35). In addition, Mbethe & Mda, (2017:5) found hepatomegaly (>4 cm) to be a common medical complication of children below five years admitted with SAM to an academic teaching hospital in Pretoria, South Africa. For these reasons, the presence of hepatomegaly was, therefore, recorded from hospital files.

xiv Oral thrush

Oral thrush normally occurs in individuals who have a compromised immune system (WHO, 1997:161). Oral thrush has been identified as associated with higher mortality especially in children with HIV. However, mortality associated with oral thrush has

also been associated with death in children with SAM regardless of HIV status. This indicates that the degree of immunosuppression or alternative reasons for immunosuppression, other than HIV, are more important than merely the identification of HIV status in patients (Rytter et al., 2017:500). For these reasons, oral thrush was recorded.

xv HIV status

HIV infection was recorded as it significantly increases mortality in children with SAM (De Maayer & Saloojee, 2011:560). Studies have also suggested that HIV-exposed, uninfected children have increased rates of death and infectious illness as well as poor growth compared with children who are HIV-unexposed (Evans et al., 2016:e92). Furthermore, a study in Kenya found that HIV was significantly associated with the development of RFS in children with SAM (Okinyi, 2018:69). HIV-exposed uninfected children, identified from maternal HIV status documented in hospital files were, therefore, recorded.

xvi Presence of tuberculosis

Tuberculosis can cause decreased appetite, nutrient and micronutrient malabsorption, and altered metabolism, which may contribute to the development of malnutrition (Gupta et al., 2009:9). In turn, TB can also be a consequence of malnutrition as malnutrition weakens the immune system, which is the primary defence against TB, therefore, increasing the host's susceptibility to infection (Cegielski & McMurray, 2004:286; De Maayer & Saloojee, 2011:560). For these reasons, the presence of TB was documented.

xvii Urinary tract infection

Urinary tract infection is a common cause of febrile illness and is the third most common bacterial infection in children (Uwaezuoke, 2016:121). Uwaezuoke's (2016:121) review of literature concerning the higher incidence of UTI in children diagnosed with SAM, found the prevalence of UTI to be high in complicated SAM, thus its presence for this study was documented.

3.5.2.5 Dietary prescription analysis

For this study, the dietary intake, phase of feeding and type of feed prescribed were recorded from available hospital files and/or NCRs for the first five days, as RFS mainly occurs within the first two to five days after initiating dietary therapy (Skipper, 2012:35; Parli et al., 2014; da Silva et al., 2020:190). If RFS occurred after this period in a specific participant, the dietary prescription was recorded for the full duration until RFS manifested. The analysis focused on determining whether there were trends associated with the development of RFS, and compared energy and protein intake to the WHO guidelines.

i Dietary intake

Dietary intake for this study, referred to energy and protein intake per kilogram, prescribed by the physician or dietitian, and was noted directly from the hospital files and/or NCRs. The reason for analysing only energy and protein intake was that the WHO dietary recommendations for the treatment of SAM during hospitalisation were based on energy and protein requirements. The reason for only analysing intake from milk and not food or breastfeeding in children with SAM (6 – 59 months) was that the WHO protocol for initial stabilisation feeding is based on energy and protein requirements per kilogram and F-75 milk-based formula only. In children younger than six months, dietary intake from expressed breastmilk and/or formula was noted if available in the hospital files and NCRs.

ii Phase of feeding

The phase of feeding was determined by comparing energy and protein intake, recorded from hospital files and/or NCRs, to the WHO recommendations (see page 30). The phase in which RFS occurred was, therefore, an important factor to determine.

iii Type of formula

Another factor that was documented was whether F-75 or an alternative formula i.e. standard, soy or hydrolysed formula, with or without modular supplements, was prescribed by the doctor or dietitian, as Namusoke et al., (2016:557) have cautioned against using F-75 substitutes because their mineral content may be sub-optimal.

3.5.3 Techniques

For the purposes of this study, the researcher followed the following procedures to capture data from the hospital files and NCRs to a datasheet:

i. **Capturing the data from hospital files and NCRs for all seemingly eligible patients, pertaining to the inclusion criteria of the study (see 3.3.2.1):**

- Weight and length/height and MUAC obtained from hospital files were recorded on the datasheet. Thereafter, weight-for-length/height was interpreted using the WHO Child Growth Standards Z-score tables (Appendix F) and MUAC was interpreted using the WHO classification for SAM by the researcher. If weight-for-length/height was <-3 SD, or MUAC was below 11.5 cm, or if bilateral pitting oedema had been recorded in the hospital files, the patient was classified as having SAM.

ii. **Capturing the data from the hospital files and NCRs for all participants finally included in the sample:**

- Weight and length/height, MUAC and the presence of pitting oedema (was already recorded on the datasheet as explained above);
- Biochemical values;
- Clinical signs and medical complications; and
- Dietary prescription as dietary intake (energy and protein intake per kilogram), phase of feeding and type of formula prescribed.

After the researcher had captured the above-mentioned data onto the datasheet, the information was transferred to Microsoft Excel for data verification and analysis.

3.6 Addressing possible measurement errors

A limitation of a study can be defined as the “systematic bias that the researcher did not or could not control and which could inappropriately affect the results” (Price & Murnan, 2013:66). For these reasons, it is important to note that all studies have limitations and the possibility of measurement errors.

According to Roberts et al. “validity describes the extent to which a measure accurately represents the concept it claims to measure” and reliability is “the proportion of variability in a measured score that is due to variability in the true score (rather than some kind of error)” (Roberts et al., 2006:42-43).

The following steps were taken to improve the validity and reliability of this study, therefore limiting possible measurement errors:

i. A datasheet compiled by the researcher was used to capture the data (Appendix D).
ii. A pilot study was performed by the researcher to test whether the datasheet was comprehensive and accurate, and captured the necessary information required for the study.
iii. Once the pilot study had been conducted, minor changes to the datasheet, aim and objectives, problem statement, biochemistry, clinical signs and medical complications, dietary prescription and title were made. Thereafter, the researcher captured the information for the period required on hard copy. This entailed that the data was manually typed from the datasheets, onto two separate Excel spreadsheets, independently by the researcher and another person, who was able to operate Excel. The two spreadsheets were then electronically sent to the Department of Biostatistics at the University of the Free State where it was compared to ensure data integrity, before analysis.

3.6.1 Possible limitations

As this was a retrospective study, the study population relied on available statistics. Prior to 1 October 2014, only the total numbers of SAM cases were recorded per month. In October 2014, a dietitian working at Rahima Moosa Mother and Child Hospital started the quarterly review of the management of SAM at the hospital using the SAM checklists which included the necessary information of a patient to be able to retrieve hospital files. However, the researcher found that not all the checklists noted in these quarterly reviews could be retrieved for analysis probably owing to hospital files having been misfiled. This led to a small sample size and thus limited the statistical analysis that could be performed.

In addition, the retrospective design of this study meant that the researcher had to rely on the information recorded in the hospital files and NCRs by others. Thus, there was no way of knowing if measurement errors had been made (such as inaccurate weighing, measuring of length/height and MUAC) by medical staff on admission; or if mistakes were made when the data was originally captured in the hospital files.

3.7 Pilot study

A pilot study can be defined as a “small study to test research protocols, data collection instruments, sample recruitment strategies, and other research techniques in preparation for a larger study” (Hassan et al., 2006:70). A pilot study is crucial in identifying possible problems and deficits in the protocol and procedures of the study before the implementation of the full study (Hassan et al., 2006:70). A pilot study was conducted to ensure that the datasheet was accurate and that the necessary data were obtained in order for the researcher to assess aspects relevant to the study and make valid interpretations of the data.

A pilot study was conducted on the first ten available hospital files and NCRs per year, from 1 October 2014 to 31 December 2018, to ensure that the datasheet was complete and included all the information that needed to be obtained and documented for this study. The pilot study was conducted once the protocol was approved by the ethics committee.

After completing the pilot study, the following amendments were submitted and approved by the HSREC (Appendix E):

- 10-Jun-2019: Minor changes made to the protocol
- 04-Sep-2019: Minor changes made to the protocol
- 20-Feb-2020: Title amended from "The incidence of hypophosphataemia and associated factors related to refeeding in children aged 0 - 59 months diagnosed with severe acute malnutrition (SAM)" to "Refeeding syndrome characterised by hypophosphataemia in children aged 0 - 59 months diagnosed with severe acute malnutrition in a South African setting"

Data obtained from the pilot study were used for analysis in the final study if there were no changes required for the study design and the data information sheet, after the pilot study.

3.8 Statistical analysis

The data analysis was generated by the Department of Biostatistics at the University of Free State using SAS software (version 9.4). (Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.). The incidence of RFS was determined for the sample under review and participants were stratified according to two outcome groups, namely those who had presented with RFS, and those who had not presented with RFS. Descriptive statistics, namely medians and percentiles for continuous data, and frequencies and percentages for categorical data were calculated per group. The probability that developing RFS was associated with biochemical, clinical and medical variables measured in the study, was calculated by stratifying the data in contingency tables. The Fischer exact test, chi-square test, and Wilcoxon's rank sum test (also known as the Mann-Whitney U test) were applied for continuous data as appropriate, and the Kruskall Wallis test for continuous data. All these tests are appropriate for unpaired data (du Prel et al, 2010).

The Fisher's exact test is used for binary data in unpaired samples and is particularly appropriate when dealing with small samples. In this study the size of the group that developed RFS was expected to be small, this the Fischer exact test was applied where a simple 2 x 2 table was required to compare the distribution of a specific measured variable between the two outcome groups (Kim, 2017:154; Du Prel et al., 2010:345).

The chi-square test is similar to the Fisher's exact test but less precise. However, it can be used to compare across more than two categories or groups. In this study, it was used to compare the distribution of variables with three or more categories between the two outcome groups. Preconditions for accuracy are that the sample size should be larger than 60 and that each cell of the contingency table contains at least 5 participants (Kim, 2017:152; Du Prel et al., 2010:345).

The Wilcoxon's rank sum or Mann-Whitney U test can be used for categorical or continuous data whether it is paired or unpaired data. It is similar to the Student's t-test for 2x2 tables but does not require the data to be normally distributed (Du Prel et al., 2010:345).

The Kruskal-Wallis test can be applied under the same conditions as the Wilcoxon rank sum test for unpaired data when comparison needs to be made across more than two categories. In this study, it was used to compare the distribution of continuous variables between the two outcome groups (Du Prel et al., 2010:345).

3.9 Challenges encountered during the execution of the study

In this study, the following challenges were encountered:

- Obtaining ethical clearance from the Gauteng Department of Health: Obtaining permission took almost a year as the building of the department was destroyed in a fire.
- Hospital files: Hospital files could only be retrieved by clerks working in the record office. For this reason, when short-staffed, collecting the hospital files for the study was understandably not a priority. So, the entire process took longer than expected. Furthermore, more than half of the hospital files could not be traced for unknown reasons. A possible explanation could be that the record department was undergoing renovation. Unfortunately, due to time constraints, the researcher was unable to repeat the process of obtaining hospital files.
- Nutrition care records: Obtaining NCRs, kept in the Department of Dietetics, was also challenging as dietitians were responsible for filing their patients' NCRs in their own cabinets. Furthermore, the SAM checklist does not indicate which dietitian saw the patient. Therefore, a process of cross-referencing the hospital files was used by the researcher in order to draw the NCRs. In addition, more than one dietitian may have seen the patient, which made some NCRs irretrievable.
- Interpreting the hospital files and recording data: Obtaining data from hospital files and NCRs were challenging as all information was handwritten by medical personnel into the files. The researcher had to search the notes for any relevant clinical signs which doctors or nurses had recorded. In the process of recording the data, it was possible to have missed appropriate information.

- Where the doctor or the dietitian had not included their calculations of the feeds in the hospital file/NCR, but only the prescription, the researcher had to calculate the nutrients from the prescription.

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CHAPTER 4: ARTICLE ONE

REFEEDING SYNDROME CHARACTERISED BY HYPOPHOSPHATAEMIA IN CHILDREN 0 – 59 MONTHS DIAGNOSED WITH SEVERE ACUTE MALNUTRITION IN A SOUTH AFRICAN SETTING

Prepared according to the guidelines for authors

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(The reference style was kept in accordance with the rest of the dissertation)

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4.1 Abstract

Background: Refeeding syndrome (RFS) is life-threatening, but an under-researched complication in the treatment of severe acute malnutrition (SAM).

Objective: To determine the incidence and onset of RFS, characterised by hypophosphataemia, and identify biochemical abnormalities, clinical signs and complications that may be associated with the development of refeeding syndrome in children aged 0 – 59 months diagnosed with SAM in a South African public hospital setting.

Methods: A retrospective analytical study was performed on retrievable hospital files of children, 0–59 months, diagnosed with severe acute malnutrition at Rahima Moosa Mother and Child Hospital, Johannesburg from 1/10/2014 to 31/12/2018. Biochemistry and clinical signs and symptoms were compared between patients who developed RFS and those who did not.

Results: The incidence of RFS among participants (63% male; median age: 34 months (IQR: 22.4) with SAM was 8.7%, with a mortality rate of 18.2%. Participants who developed RFS stayed in hospital significantly longer (18 vs 12 days) (p=0.003) and, on admission, a significantly higher percentage of participants with RFS presented with hypophosphataemia (p=0.04), moderate to severe hypokalaemia (p=0.0005), hyponatraemia (p = 0.004), international normalised ratio >1.7 (p=0.049), dehydration (p=0.03), and urinary tract infection (p=0.04) than those who did not have RFS. Oedema was more prevalent on admission in the RFS-group (63.6% vs 39.1%), though not statistically significant. Overall, 20% (n=23) had human immunodeficiency virus, but none of these patients developed RFS.

Conclusion: This study identified low levels of electrolytes, elevated international normalised ratio, and the presence of dehydration and urinary tract infection on admission as significantly associated with developing RFS despite the implementation of World Health Organisation (WHO) treatment guidelines in a South African setting.

Keywords: Refeeding syndrome, hypophosphataemia, severe acute malnutrition, paediatrics, South Africa

4.2 Introduction

Severe acute malnutrition is a term used by the WHO in children under five years of age to indicate severe undernourishment, and is diagnosed by the occurrence of either: severe wasting i.e. weight-for-length/height <-3 standard deviation (SD) on the WHO growth standards; a mid-upper arm circumference (MUAC) <11.5 cm in children between 6 – 59 months; or the presence of bilateral pitting oedema (WHO, 2013b:2, 63). Undernutrition, referred to as malnutrition in this paper, is the cause of about 45% of deaths worldwide in children below five years (WHO, 2020a). Hospitals can, however, reduce their case-fatality rate related to SAM to < 10% by following the WHO management guidelines (Tickell & Denno, 2016:642). Tickell & Denno (2016:648) have, however, highlighted that the treatment guidelines for SAM were developed mainly based on expert opinion rather than scientific evidence and believe that the guidelines and outcomes of patients could be improved based on the findings of additional clinical and epidemiological research (Tickell & Denno, 2016:648). An additional problem contributing to the fatality rate in malnourished children is the fact that these patients receiving nutritional treatment are at risk of developing a life-threatening complication known as RFS (Afzal et al., 2002:515; Boateng et al., 2010:156; Rytter et al., 2017:494; Mbethe & Mda, 2017:1; Okinyi, 2018). Although the WHO has addressed this complication by providing guidelines that reduce the risk of its development through transition phase feeding, however, the lack of research and evidence in this field makes it difficult to determine whether the approach of transition phase feeding can be improved. (WHO, 2013b:41). Furthermore, regarding electrolyte supplementation, Brewster (2011:97) has suggested that phosphate supplementation should be added to the WHO protocol to prevent RFS.

To complicate matters further, diverse sets of dietary guidelines have been developed (Afzal et al., 2002; WHO, 2013b; Meyer & Marino, 2015; O'Connor & Nicholls, 2015; da Silva et al., 2020), independent of each other for the treatment of SAM and RFS.

Refeeding syndrome is a metabolic condition that occurs after initiating feeds, particularly those high in carbohydrates, in a catabolic, starved patient which subsequently triggers a sudden shift in metabolism (catabolism to anabolism) leading to fluid and electrolyte disturbances which are significantly associated with increased

mortality (Stanga et al., 2008:687; Wagstaff, 2011:505; Friedli et al., 2020b:140; Friedli et al., 2020b). The onset of the syndrome has predominantly been characterised by hypophosphataemia (a drop in phosphate to below normal levels) within days of initiating nutritional therapy (Friedli et al., 2020b:136; da Silva et al., 2020:2). Research of RFS in children with severe malnutrition has mainly investigated the occurrence of hypophosphataemia (Yoshimatsu et al., 2013; Hother et al., 2016; Namusoke et al., 2016; Rytter et al., 2017), and then associated it with RFS, without defining RFS per se. The reason for this could possibly be due to the absence of a universally accepted definition for RFS (da Silva et al., 2020:2). Furthermore, only two studies in Africa have determined the incidence of RFS in children admitted with SAM (Mbethe & Mda, 2017; Okinyi, 2018). In the first study, undertaken in 2017 in a South African public hospital, Mbethe & Mda determined that the incidence of RFS in children below five years with SAM, following the WHO management protocol, was 15% based on a blood phosphate value < 1 mmol/L on the fifth day of hospitalisation (Mbethe & Mda, 2017). The second study was conducted in Kenya where Okinyi (2018:69) determined that the incidence of RFS in children aged six months to five years admitted with SAM was 21%. The exact management on participating children was not described, but Okinyi mentioned that the participants received F-75. Okinyi diagnosed RFS as a drop in blood phosphate or potassium by >0.3 mmol/L from baseline values. The findings of the mentioned studies confirm the ambiguity in the diagnosis criteria of RFS, which highlights the difficulty of determining the true incidence of RFS due to the lack of a standardised definition.

Particularly relevant to the South African setting is the fact that very little is known about the impact of human immunodeficiency virus (HIV) as a comorbidity in the management of SAM (Biggs, 2013:176). Also, sparse information is available on the specific risk factors that may predispose a severely malnourished child to develop RFS in a population with a high prevalence of HIV. Therefore, it is vital to identify RFS in a setting where children with SAM may also be HIV positive, to furthering the research in this field. To prevent and manage this potentially fatal condition, early diagnosis is crucial, and ongoing research is, therefore, essential to address the many inconsistencies in defining and treating the syndrome (Tresley & Sheean, 2008:2105; Crook, 2014:1448; Friedli et al., 2017:159).

This study aimed to determine the incidence and onset of RFS, characterised by hypophosphataemia, in a South African setting among children aged 0 – 59 months who were diagnosed with SAM. The study also explored biochemical abnormalities, clinical signs and medical complications that may be associated with the development of RFS in patients admitted with SAM. In addition, further research may assist in the early identification of patients admitted with SAM who are more likely to develop RFS, and may motivate for a more cautious approach to treating this sub-group of SAM patients.

4.3 Methods

4.3.1 Study design, setting and study population

A retrospective analytical cohort study of retrievable hospital files of children aged 0 – 59 months admitted with SAM to Rahima Moosa Mother and Child Hospital, Coronationville, Johannesburg, South Africa, from 1 October 2014 to 31 December 2018, was conducted.

Ethics approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State. Permission was also obtained from the Gauteng Department of Health and from the hospital management to perform the study and to retrieve retrospective information from hospital files kept by the hospital for the review period. All retrieved data were kept confidential.

4.3.2 Sampling

According to electronic statistics kept by the Dietetics Department of the hospital, 592 children with SAM were admitted during the period under review. In the hospital, a “tick box” summary of the WHO 10-step protocol, known as a SAM checklist, was added to the hospital file of each SAM patient on admission. The dietitian routinely completed the SAM checklist and files it in the Dietetics Department. Only 329 (56%) SAM checklists could be traced and of these 329 checklists, only 148 (25%) hospital files could be retrieved from the Hospital Archives Department by the responsible clerks.

The diagnosis of SAM was verified by the researcher by applying the following WHO criteria to data captured in the retrieved hospital files: weight-for-length/height <-3 SD (https://www.who.int/childgrowth/standards/weight_for_length_height/en/), or a MUAC < 11.5 cm in children older than six months, or the presence of bilateral pitting oedema. The diagnosis of SAM could be confirmed for 126 patients who were then eligible for inclusion in the study. The sample thus represented only 21% of the patients listed as admitted with SAM to the hospital during the time under review.

4.3.3 Data collection

In addition to the weight, length/height, MUAC, and the presence of bilateral pitting oedema on admission to confirm the diagnosis of SAM as noted above, date of birth, gender, ethnicity, country of origin, date of admission, date of discharge, and date of death, were recorded from the hospital files. These variables were used to determine the age, length of hospital stay, weight gain during hospitalisation, number of deaths, and time to death. All biochemical values associated with SAM, RFS, or the prognosis of a patient, that were recorded in the hospital files were captured including blood levels of phosphorus, potassium, magnesium, calcium, sodium, urea, creatinine, haemoglobin, platelets, C-reactive protein (CRP), international normalised ratio (INR), total bilirubin, alanine aminotransferase, alkaline phosphatase, and aspartate aminotransaminase (Tadesse et al., 2010:18; De Maayer & Saloojee, 2011:3; Stevens et al., 2013:e17; Gebremichael, 2015:4; Rytter et al., 2017:500; da Silva et al., 2020). Finally, any clinical signs and medical complications that were recorded in the hospital files on day one of hospitalisation which included vomiting, diarrhoea or acute gastroenteritis (AGE), dehydration, dermatosis, hypoglycaemia, hyperglycaemia, hypothermia, pneumonia, respiratory complications such as acute respiratory distress, sepsis, septic shock, loss of appetite, nasogastric tube feeding (NGT), hepatomegaly, oral thrush, HIV infection, exposure to HIV, tuberculosis (TB) and urinary tract infection (UTI), were documented.

4.3.4 Data analysis

Refeeding syndrome was defined in this study as a drop in blood phosphate levels by $\geq$ 0.16 to a value $\leq$ 0.65 mmol/L, after initiation of feeds, based on the definition of Marik and Bedigian (1996:1044). At the time of the study, this classification was one of the most frequently used definitions of RFS according to the systematic review of

Friedli et al. (2017:153-154). The incidence of RFS in the sample was determined and the sample was stratified into participants who developed RFS (the RFS-positive group), and those who did not develop RFS (the RFS-negative group). Medians and percentiles were used to describe numerical data, and frequencies and percentages to describe categorical data in the total sample and within the groups. The groups were compared by means of contingency tables applying the Kruskal-Wallis test for numerical data and Fisher's exact or Chi-square for categorical data, as applicable, to determine significant differences and associations. A p-value of <0.05 was considered statistically significant.

4.4 Results

The study included 126 participants with confirmed SAM based on the WHO definition. Of the sample, 11 (8.7%) participants developed RFS during their hospital stay after feeding was initiated. The demographic data (Table 4.1) for the whole sample was stratified according to the development of RFS (RFS-positive and RFS-negative groups). As a whole, the sample had a median age of 34.2 months (IQR: 22.4) and were mostly males (62.7%), of African descent (95.2%) and from South Africa (64.3%) and Zimbabwe (21.4%). The participants in the RFS-positive group were predominantly male, African, and mainly from South Africa and Zimbabwe. No significant differences in these variables were present in the RFS-negative group.

Mortality of 15.1% was calculated for the sample (n=19/126) and 18.2% (n=2) in the RFS-positive group, with no statistical significant difference compared to 14.8% (n=17) in the RSF-negative group (Table 4.1). The overall median time until death was nine days (IQR: 13) and did not differ significantly between the RFS-positive group (14 days; IQR: 10) and the RFS-negative group (7 days; IQR: 7).

Table 4.1: Demographic data of the participants, stratified according to the development of RFS

Variables and categories		All (n=126)		RFS-positive group (n=11)		RFS-negative group (n=115)		P-value
		n	%	n	%	n	%	
Gender **(n=126)**	Male	79	62.7	7	63.6	72	62.6	1.00
	Female	47	37.3	4	36.4	43	37.4	
Ethnicity **(n=126)**	White	0	0.0	0	0.0	0	0.0	0.70
	African	120	95.2	11	100	109	94.8	
	Coloured	4	3.2	0	0.0	4	3.5	
	Indian	2	1.6	0	0.9	2	1.7	
Nationality **(n=111)**	South Africa	72	64.3	5	55.6	67	65.1	1.00
	Zimbabwe	24	21.4	3	33.3	21	20.4	
	Mozambique	8	7.1	1	11.1	7	6.8	
	Malawi	4	3.6	0	0.0	4	3.9	
	Pakistan	1	0.9	0	0.0	1	1.0	
	India	1	0.9	0	0.0	1	1.0	
	Congo, DRC	1	0.9	0	0.0	1	1.0	
Mortality (n=126)		19	15.1	2	18.2	17	14.8	0.28

The anthropometry on admission and duration of hospital stay are summarised in Table 4.2. On admission, the overall sample had a median weight of 6.3 kg, median length/height of 69 cm, and median MUAC of 11.1 cm. MUAC was recorded for less than half of the participants (n=60; 47.6%). On admission, the RFS-positive group was younger, shorter and weighed less than the RFS-negative group (9.4 months; IQR: 9.6) months compared to 12.8 (IQR: 12.8) months; 5.6 (IQR: 2.6) kg compared to 6.4 (IQR: 2) kg; and 67.5 (IQR: 8) cm compared to 69 cm (IQR: 12.5). MUAC on admission in the RFS-positive group was 11.2 cm (IQR: 2.5) compared to 11.1 cm (IQR: 2.2) in the RFS-negative group. However, none of the anthropometrical indices were significantly different between the groups.

The median overall duration of hospitalisation was 12 days (IQR: 9). The median stay in hospital was significantly longer (p = 0.003) for the RFS-positive group (18 days; IQR: 12) than the RFS-negative group (12 days; IQR: 9). During hospital stay, participants gained a median weight of 0.6 kg (IGR: 0.7) to reach a median weight of 7.1 kg on discharge. The RFS-positive group gained more weight during hospitalisation (0.9 kg; IQR: 0.2) compared to 0.5 kg (IQR: 0.7) in the RFS-negative group, but weighed less on discharge (6.9 kg; IQR: 1.6) compared to 7.1 kg (IQR: 2.2) in the RFS-negative group. Furthermore, the RFS-positive gained a median weight of

7.7 g/kg/day (IQR: 3.9) compared to 7.2 g/kg/day (IQR: 7.4) in the RFS negative group. These differences were not statistically significant.

Table 4.2: Anthropometry and duration of hospital stay of the participants, stratified according to the development of RFS

	All (n=129)			RFS-positive group (n=11)			RFS-negative group (n=129)			P-value
	n	Median	P25;P75¥	n	Median	P25;P75	n	Median	P25;P75	
Age on admission (months)	126	34.2	26.0; 48.4	11	9.4	8.1; 17.8	115	12.8	7.7; 19.7	0.95
Weight on admission (kg)	126	6.3	5.3; 7.3	11	5.6	4.7; 7.3	115	6.4	5.3; 7.3	0.45
Length/height on admission (cm)	121	69.0	65.0; 77.0	10	67.5	62.0; 70.0	111	69.0	65.0; 77.5	0.46
MUAC on admission (cm)	60	11.1	10.4; 12.5	4	11.2	10.3; 12.7	56	11.1	10.4; 12.5	0.95
Duration of hospitalisation (days)	125	12	8; 17	11	18	15; 27	114	12*	7; 16	0.003*
Weight on discharge (kg)	105	7.1	6.1; 8.3	9	6.9	6.0; 7.6	96	7.1	6.4; 8.3	0.75
Weight gain during hospitalisation (g/kg/day)	105	0.6	0.2; 0.9	9	0.9	0.8; 1.0	96	0.5	0.2; 0.9	0.25
Time until death (days)	19	9	2;15	2	14	9; 19	17	7	2; 15	0.29

*p<0.05 was considered significant

Regarding the diagnostic criteria of SAM, participants were stratified according to those that presented with oedema and those that did not present with oedema i.e. severe wasting (weight-length/height <-3SD or MUAC <11.5 cm in children over six months) for the total sample and both groups (Figure 4.1). The majority of participants in the total sample (n=75; 59.5%), as well as in the RFS-negative group (n=70; 60.9%) presented with severe wasting on admission. On the contrary, it is noteworthy that the majority of participants in the RFS-positive group (n=7; 63.6%) presented with oedema on admission, however, the difference between the RFS- positive and RFS-negative groups was not statistically significant.

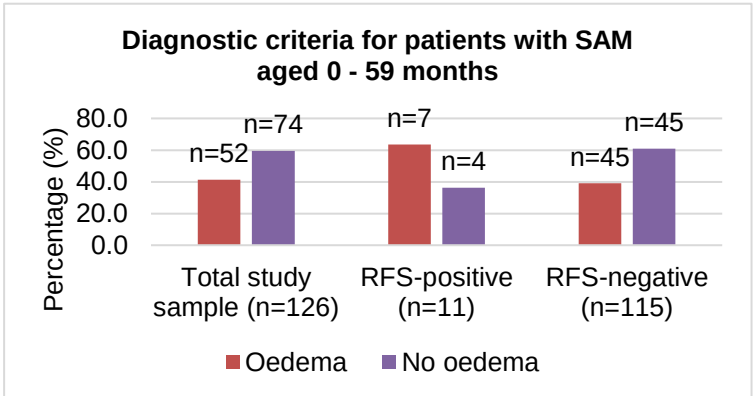

Figure 4.1: Diagnostic criteria of children with SAM between 0 - 59 months

Table 4.3 summarises the biochemical data, showing that a significantly larger percentage of participants in the RFS-positive group had hypophosphataemia (p=0.03), moderate to severe hypokalaemia (0.0005), hyponatraemia (p=0.004), and elevated INR (p=0.049) on admission compared to the RFS-negative group. There were no significant differences between the two groups concerning the percentage of participants with hypomagnesaemia, hypocalcaemia, anaemia, thrombocytopaenia, elevated CRP, elevated urea and creatinine, or deranged liver enzymes on day one of hospitalisation.

Table 4.3: Biochemical findings on admission

Classification	Diagnostic criteria for classification		RFS-positive group		RFS-negative group		P-value
			n	%	n	%	
Hypophosphataemia	< 1 year	< 1.3 mmol/L	10	60	90	21	0.03*
	1 – 16 years	< 0.9 mmol/L					
Moderate hypokalaemia	Paediatric[1]	< 3.5 mmol/L	10	40	102	25.5	0.0005*
Severe hypokalaemia		< 2.5 mmol/L	10	50	102	10.8	
Hypomagnesaemia	Paediatric	< 0.6 mmol/L	0	0	1	1.1	0.44
Moderate to severe hypomagnesaemia		< 0.5 mmol/L	0	0	1	1.1	
Hypocalcaemia	< 4 weeks	< 2.0 mmol/L	10	60	91	64.8	0.74
	4 weeks – 16 years	< 2.2 mmol/L					
Hyponatraemia	Paediatric[1]	< 133 mmol/L	10	70	103	18	0.004*
Hypoalbuminaemia	< 4 weeks	< 25 g/L	10	90	93	73.1	0.55
	4 weeks – 1 year	< 30 g/L					
	1 – 16 years	< 35 g/L					
Elevated CRP (risk for death)	Paediatric[1]	> 15 mg/L	9	66.7	95	56.8	0.50
Elevated urea	0 – 12 months	> 5.5 mmol/L	10	30	103	24.3	0.91
	1 – 16 years	> 6.5 mmol/L					
Elevated creatinine	Neonate[2]	> 75 µmol/L	10	40	102	29.4	0.47
	1 month – 4 years	> 39 µmol/L					
Elevated bilirubin	14 days – 16 years	> 21 µmol/L	9	11.1	72	8.3	0.58
Elevated ALP	Neonate[2]	> 391 IU/L	9	22.2	74	4.1	0.17
	Infant[3]	> 425 IU/					
	1 – 14 years	> 308 IU/L					
Elevated GGT	Paediatric[1]	> 40 IU/L	9	88.9	72	55.6	0.08
Elevated ALT	0 – 12 months	> 41 IU/L	9	66.7	73	50.7	0.49
	1 – 2 years	> 28 IU/L					
	3 – 6 years	> 29 IU/L					
Elevated AST	Neonate[2]	> 92 IU/L	9	44.4	73	48	1.00
	Child[4]	> 60 IU/L					
Anaemia	6 – 59 months	< 11 g/dl	10	60	91	68.1	0.65
Severe anaemia		< 7 g/dl	10	10	91	7.7	
Thrombocytopaenia	Paediatric[1]	< 150 (×10^3/µl)	10	10	89	11.2	0.58
Elevated INR (poor prognostic factor for death)	Paediatric[1]	>1.7	8	63	44	20	0.049*

*p<0.05 was considered significant; [1] 0 – 14 years; [2] < 28 days; [3] 28 days – 1 year; [4] 1- 14 years

Table 4.4 summarises clinical signs and symptoms possibly associated with SAM or RFS, that occurred on day one of admission and had been recorded in the hospital files. A significantly higher percentage of participants in the RFS-positive group presented with dehydration (p=0.03) and UTI (p=0.04) on the first day of hospitalisation compared to the RFS-negative group. HIV-exposure was borderline significant (p=0.05) and the presence of diarrhoea on admission had a trend towards significance (p=0.06) in the RFS-positive group. The presence of vomiting, AGE, dermatosis, hypoglycaemia, hypothermia, hyperglycaemia, pneumonia, respiratory complications, sepsis, septic shock, loss of appetite, nasogastric tube feeding, hepatomegaly, oral thrush, HIV infection and TB did not significantly differ between the two groups.

Table 4.4: Clinical signs and medical complications on admission

Clinical signs and medical complications	n	RFS-positive group		RFS-negative group		p-value
		n	%	n	%	
Vomiting	126	7	63.6	52	45.2	0.35
Diarrhoea	126	9	81.8	57	49.6	0.06
AGE	126	8	72.7	59	51.3	0.22
Dehydration	126	9	81.8	53	46.1	0.03*
Oedema	126	7	63.6	45	39.1	0.20
Dermatosis	126	5	45.5	34	29.6	0.31
Hypoglycaemia (< 3 mmol/L)	125	3	27.3	10	8.8	0.09
Hyperglycaemia (>7 mmol/L)	125	4	36.4	37	32.5	0.75
Hypothermia	126	1	9.1	1	0.9	0.17
Pneumonia	126	4	36.4	42	36.5	1.00
Respiratory complications[1]	126	6	54.6	48	41.7	0.53
Sepsis	126	4	36.4	18	15.7	0.10
Septic shock	126	1	9.1	6	5.2	0.48
Loss of appetite	126	8	72.7	68	59.1	0.52
Nasogastric tube feeding	126	4	36.4	24	20.9	0.26
Hepatomegaly	126	6	54.6	41	35.7	0.33
Oral thrush	126	1	9.1	24	20.9	0.69
HIV infection	126	0	0.0	23	20.0	0.21
HIV exposed	126	2	18.2	61	53.0	0.05
TB	126	1	9.1	16	13.9	1.00
UTI	126	5	45.5	20	17.4	0.04*

*p<0.05 was considered significant

[1] dyspnoea/respiratory distress, respiratory failure, ventilatory dependency and or diaphragm/intercostal muscle Weakness

4.5 Discussion

This study determined that the incidence of RFS in participants aged 0 – 59 months admitted to Rahima Moosa Mother and Child Hospital with SAM, was 8.7%, of which 18.2% died. Participants in the RFS-positive group has significantly more hypophosphataemia, hypokalaemia, hyponatraemia, dehydration, INR >1.7 and UTI on admission, and had a significantly longer length of hospitalisation compared to participants who did not develop RFS.

The median age of participants in the RFS-positive group was 9.4 months compared to 12.8 months in the RFS-negative group. However, the age difference was not significantly different. This finding differs to a similar South African study which reported a mean age of 15.0 months for participants with SAM who developed RFS compared to 16.3 months in participants who did not (Mbethe and Mda, 2017:3). Furthermore, this study found that the majority of participants in both RFS-positive and RFS-negative groups were male (63.6% vs 62.6%). This confirms the finding of Svedberg's extensive analysis on gender bias in undernutrition in four sub-Saharan African countries namely Swaziland, Liberia, Cameroon and Lesotho which identified that stunting and wasting were slightly higher in pre-school boys than girls (Svedberg, 1990:471). Similar outcomes were found in more recent studies, with similar objectives to the study under review. These studies showed slight male predominance in the incidence of RFS in SAM in South Africa and Kenya (Mbethe and Mda, 2017:3; Okinyi, 2018:70).

RFS occurred in 8.7% of participants below five years admitted with SAM in this study, based on one of the more commonly used definitions at the time of data collection namely that RFS occurred if blood phosphate levels dropped by 0.16mmol/L to a value below 0.65 mmol/L (Marik (1996:1044) cited by Friedli *et al.*, 2017:153). The incidence of RFS in this study was notably lower than in two other studies which also determined the incidence of RFS in children below five years admitted with SAM. Firstly, Mbethe & Mda, (2017) determined an incidence of 15% based on a blood phosphate value of less than 1 mmol/L on the fifth day of hospitalisation (Mbethe & Mda, 2017). Secondly, Okinyi, (2018), determined an incidence of 21% based on a drop in blood phosphate or potassium by more than 0.3 mmol/L from baseline values.

The absence of a standardised definition for RFS (da Silva *et al.*, 2020:2) confounds the comparison of the incidence of RFS between different studies and different settings.

A large randomised trial, which included 967 participants, admitted to Kantonsspital Aarau and University Hospital Bern in Switzerland, who were classified at nutritional risk and were likely to be admitted for more than five days, determined that patients who develop RFS have poorer outcomes and a significantly increased risk of death (Friedli et al., 2020a:1; Friedli et al., 2020b:140). In this study, 18.2% of participants that developed RFS, died within a median time of 14 days. However, this may not be a true representation of the study population as 91.7% (n=24) of hospital files of participants who demised could be obtained, compared to only 37.7% (n=124) of hospital files for those who were discharged from hospital, indicating retrieval bias. The only other South African study on RFS in children with SAM reported that 6% of participants with SAM who developed RFS died (Mbethe and Mda, 2017). Furthermore, in Kenya, a study reported 3% of children with SAM who developed RFS died (Okinyi, 2018:71). Other studies have investigated death associated with hypophosphataemia in children with malnutrition. Kimutai *et al.*, (2009:330), reported that 8%, 14% and 21% of deaths were associated with mild, moderate and severe hypophosphataemia respectively, in children with kwashiorkor and marasmic kwashiorkor. An older study from Malawi showed that 7% of deaths in children with kwashiorkor were found to be associated with severe hypophosphataemia (Manary, Hart and Whyte, 1998:791).

Studies have mainly investigated biochemical changes and clinical signs and symptoms that are associated with the occurrence of RFS, but not many have investigated factors on admission that may be associated with its development. Biochemical abnormalities which occurred on day one of admission that were significantly more prevalent in those participants who developed RFS in this study were hypophosphataemia (p=0.03), moderate to severe hypokalaemia (p=0.0005), hyponatraemia (p=0.004) and INR >1.7 (p=0.049). Hypophosphataemia, hypokalaemia and hypomagnesaemia are common electrolyte imbalances that occur as a result of RFS (Stanga *et al.*, 2008:687; Friedli *et al.*, 2017:152; da Silva et al., 2020:180). In addition, hypokalaemia and hypomagnesaemia occur frequently in

children with SAM as a result of muscle loss and kidney dysfunction subsequent to reductive adaptations during starvation (WHO, 2004:35-36). Decreased blood levels of phosphorus, potassium and magnesium before initiation of nutritional therapy have recently been identified as risk factors for developing RFS by the American Society for Parenteral and Enteral Nutrition (ASPEN) (da Silva *et al.*, 2020:11-12). The significant association between hypophosphataemia and hypokalaemia on admission and the onset of RFS was similar to findings by Mbethe and Mda (2017:5). In their study, hypokalaemia on admission was also significantly associated with RFS, while blood phosphate levels on admission were significantly lower in children who later developed RFS than those who did not (Mbethe & Mda, 2017:5).

Hyponatraemia was significantly more prevalent on admission in this study in participants who later developed RFS (p=0.004). However, Mbethe and Mda (2017:5) did not find a significant difference in sodium values on admission between those who developed RFS and those who did not. Hyponatraemia normally occurs as a result of hyperglycaemia which occurs during RFS, as sodium and glucose are co-transported (Khan et al., 2011:2; Skipper, 2012:34). However, hyponatraemia has not yet been associated with the development of the syndrome. Hyponatraemia is, however, a common finding in children with SAM (Raza et al., 2020:2). Despite the low blood levels of sodium, children with SAM, especially oedematous SAM, actually have a surplus of body sodium. This occurs due to the kidney's inability to excrete sodium sufficiently as a result of reductive adaptations which occur during starvation. The build-up of sodium leads to the accumulation of water which masks the surplus total body sodium levels (WHO, 2004:34-35; Raza et al., 2020:2). Furthermore, hyponatraemia is associated with diarrhoea in children with SAM (Zogg et al., 2013:402). In the current study, the presence of diarrhoea on admission showed a trend towards being significantly associated with the development of RFS (p=0.006).

International normalised ratio is used to evaluate coagulation status and the risk of bleeding in a patient with an increased INR indicating prolonged clotting time (Shikdar & Bhattacharya, 2019:1). An elevated INR is an indication of acute liver failure and is the consequence of the liver not being able to synthesise vitamin K-dependent clotting factors (Crismale & Friedman, 2020:655). A South African study investigating clinical outcomes in malnourished children with or without HIV infection found that INR >1.7

was significantly associated with an increased risk of death in children admitted with kwashiorkor (De Maayer and Saloojee, 2011:3). In this study, A significantly higher percentage of participants in the RFS-positive group presented with an INR >1.7 on admission compared to the participants in the RFS-negative group (p=0.049). To date, no study has investigated INR as a risk factor for the development of RFS in SAM. A possible reason for elevated INR in SAM could be due to reductive adaptations which occur as a result of severe food shortage and involves alterations in physiology and metabolism. Thus, reduced growth and physical activity, and a decrease in basal metabolic rate occur to preserve energy and maintain life as far as possible (WHO, 2004:34). The liver is one of the many organs that undergo adaptations such as reduced gluconeogenesis and production of transport proteins which consequently lead to liver dysfunction (WHO, 2004:35). International normalised ratio might, therefore, be an important predictor of the severity of SAM and development of RFS, but more research in this regard is required.

With regard to clinical signs and medical complications, oedema, which is also an independent diagnostic clinical sign for the diagnosis of SAM, can be a life-threatening complication of SAM (WHO, 2013:14; Rytter *et al.*, 2015:1). The degree of oedema in children with SAM ranges from having “simple nutritional oedema to fulminant kwashiorkor, with anaemia, hepatomegaly, mental changes and dermatosis” (Rytter *et al.*, 2015:1). A higher percentage of participants who developed RFS in this study had oedema (63.6%) on admission compared to those who did not develop RFS (38.3%), although the difference was not significant (p=0.2). This finding differs from that of a South African study, where RFS was significantly associated with oedema in children hospitalised with SAM, despite having only 104 participants in their study (Mbethe and Mda, 2017:6). Furthermore, in a study in Uganda, below normal plasma phosphate levels were associated with death in children with oedematous SAM (Rytter *et al.*, 2017:500). The authors concluded that RFS could develop in children undergoing treatment for SAM, who present with hypophosphataemia, especially in children with oedema (Rytter et al., 2017:494). The available literature, therefore, has identified oedematous SAM not only as life-threatening but also associated with higher death rates, related to low phosphate levels in children with SAM. Hypophosphataemia, before initiating feeding, is, therefore, an important clinical sign to consider when identifying children who are at risk of developing RFS.

Moreover, in the current study, significantly more participants in the RFS-positive group presented with dehydration on admission than in the RFS-negative group (p=0.03). This may be related to the presence on admission of diarrhoea, a major cause of dehydration, which showed a trend towards being significantly associated with RFS (p=0.06), Children with SAM are prone to diarrhoea (Mwangome *et al.*, 2011:1), and to acute gastroenteritis (AGE), characterised by "acute diarrhoea, nausea, vomiting, fever, and abdominal pain" (Colletti et al., 2010:686). Mbethe and Mda (2017:6) also found diarrhoea to be significantly associated with RFS, although they did not assess dehydration. Furthermore, diarrhoea in children with SAM has also been associated with hyponatraemia, whereas hyponatremia on admission was significantly associated with RFS-positive group in this study (Zogg et al., 2013:402). Manary et al., (1998:790) showed a significant association between dehydration and severe hypophosphataemia. Kimutai et al., (2009:331), however, did not find dehydration to be significantly associated with RFS.

Furthermore, significantly more participants in the RFS-positive group had UTI was on admission compared to participants in the RFS-negative group (p=0.04). UTI is a common cause of febrile illness in children and is more common in children with SAM (Uwaezuoke, 2016:121). At the time of this study, the researcher could not find literature to support that UTI is associated with RFS.

Particularly relevant in South Africa is that HIV not only contributes to the development of malnutrition, but has also been significantly associated with an increased risk of death in patients with SAM (De Maayer and Saloojee, 2011:1,3). Although Okinyi (2008:69,71) found a significant association between the development of RFS and the presence of HIV infection, this study did not find any association. However, the current study did show a borderline significant association between HIV-exposure and the onset of RFS (p=0.05). This is an interesting association which could be related to other studies that have linked HIV-exposure to increased rates of death, infectious illness, as well as poor growth in infants (Evans et al., 2016:e92).

When considering the length of hospital stay, participants who developed RFS had a significantly longer duration of hospitalisation (p = 0.003) compared to those who did not develop RFS. However, no paediatric studies reporting the length of stay related to RFS could be found by the researcher at the time of this study However, Friedli et

al. (2020a:1) determined, in their randomised trial of 967 older adults, that RFS was associated with a prolonged length of hospitalisation.

The average weight gain during hospitalisation for the participants with RFS was 0.9 kg and 0.5 kg for those without RFS. Furthermore, the median weight gain per day was higher in the RFS-positive group (7.7g/kg/day; IQR: 3.9) compared to 7.2 g/kg/day (IQR: 7.4) in the RFS-negative group, indicating a median moderate weight gain per day for both groups. These differences were, however, not statistically significant and the slightly higher weight gain in the RFS-positive group may have been attributed to the longer length of hospitalisation.

Therefore, the fact that hypophosphataemia, hypokalaemia, hyponatraemia, INR >1.7, dehydration and UTI were significantly more prevalent on admission in participants who developed RFS are important considerations when screening children with SAM on admission. Furthermore, it is concerning that in current practice, physicians, especially those who are inexperienced, have trouble recognising and treating RFS as their awareness of the syndrome is limited (Friedli et al., 2020b:138). More research in larger samples is essential to confirm whether these findings are associated with the development of RFS, and also to increase awareness of the syndrome and possibly improve current treatment protocols.

4.6 Limitations

Due to the retrospective design, an unforeseen limitation of this study was the difficulty in obtaining hospital files, possibly due to misfiling or other unknown logistical problems producing a small sample size. In addition, the researcher had to rely on the information recorded in the hospital files and NCRs completed by others. Thus, there was no way of knowing if measurement errors such as inaccurate weighing, measuring of length/height and MUAC, had been made by medical personnel on admission, or if errors were made when the data were originally captured in the hospital files. In addition, the small number of participants with HIV in the current small sample made it difficult to make meaningful conclusions regarding the risk factors for RFS in an HIV setting.

4.7 Conclusion and recommendations

Refeeding syndrome occurs in children with SAM, despite the implementation of the current WHO medical and nutritional management recommendations. However, F-75 substitutes (commercial infant formulas with additional modular supplementation to increase the energy content as well as individually prescribed electrolytes and vitamin and mineral supplementation as per the WHO protocol) were used in the nutritional management of patients in this study, which deviates from the WHO protocol.

General risk factors for the development of RFS exist, but further research is undoubtedly needed to determine risk factors for the development of RFS in specific diagnoses, especially in SAM, as children with SAM are vulnerable and are already at risk of death. In addition, RFS being significantly associated with increased mortality (Friedli et al., 2020a:1) therefore, contributes to the already high rate of deaths associated with childhood undernutrition. Furthermore, hypophosphataemia, hypokalaemia, hyponatraemia, INR >1.7, dehydration and UTI may be risk factors for developing RFS in children with SAM on admission as identified in this study, however, more research on larger samples would be necessary to confirm these findings and possibly identify additional risk factors. Decreased blood levels of phosphorus, potassium and magnesium before nutritional intervention have, however, recently been identified as risk factors for developing RFS (da Silva *et al.*, 2020:11-12). The addition of phosphate to the existing WHO protocol, also suggested by Brewster, (2011:97) may, therefore, be beneficial in decreasing the occurrence of RFS.

Further research into the clarification of the definition of RFS is vital to determine the true incidence of the syndrome and also to increase awareness of the syndrome in clinical practice. Two consensus definitions for the diagnosis of RFS have recently been published, which might contribute to a clearer direction for the diagnosis. Firstly, Friedli et al. (2018) suggest defining RFS “based on electrolyte concentrations and clinical symptoms, imminent and manifest RFS may be distinguished. Imminent RFS is present if the shift in electrolytes (decrease of phosphate from baseline >30% or below 0.6mmol/l or any two other electrolyte shifts below normal range) occurs within 72 hours after the start of nutrition therapy, while manifest RFS is considered if any electrolyte shifts occur in conjunction with typical clinical symptoms”. Secondly, da

Silva et al.,(2020:190) have proposed the following definition: “A decrease in any 1, 2, or 3 of serum phosphorus, potassium, and/or magnesium levels by 10%–20% (mild RFS), 20%–30% (moderate RFS), or >30% and/or organ dysfunction resulting from a decrease in any of these and/or due to thiamine deficiency (severe RFS); and occurring within 5 days of reinitiating or substantially increasing energy provision”.

Being able to identify children who are more likely to develop RFS and diagnose them appropriately can lead to better management of this vulnerable sub-group of children with SAM, and improve clinical outcomes. Furthermore, it is recommended that research about diagnosis criteria, prevention guidelines and medical and nutritional treatment of RFS, could contribute to the improved management of children with SAM.

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CHAPTER 5: ARTICLE TWO

DIETARY FACTORS ASSOCIATED WITH REFEEDING SYNDROME IN CHILDREN WITH SEVERE ACUTE MALNUTRITION IN A SOUTH AFRICAN PUBLIC HOSPITAL

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5.1 Abstract

Objective: To identify dietary factors associated with the development of refeeding syndrome (RFS) in children admitted with severe acute malnutrition (SAM)

Design: Retrospective analytical cohort study

Setting: Paediatric wards at Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa.

Subjects: 126 participants, 0 – 59 months, with severe acute malnutrition

Outcome measures: Feeding history compared between those who developed RFS, and those who did not.

Results: The incidence of RFS was 8.7% (n=11). For those who developed RFS, median energy and protein intake during the first five days of hospitalisation were 76.2 kcal/kg and 1.3 g/kg, respectively, compared to 89 kcal/kg and 1.5 g/kg, respectively, for those who did not. Most participants who developed RFS (90.9%) were in the initial phase of feeding, with only one participant in the transition phase according to their energy and protein intake. Of those that developed RFS, 45.5% did so within 3-5 days; the rest within 6-13 days after feeding was initiated. At diagnosis of refeeding syndrome, 64.5% were receiving standard commercial formula, 27.3% hydrolysed formula, and 9.1% soy or F-75 formula. On admission, oedema was more prevalent in participants who developed RFS (63.6%) than those who did not (38%) and 81.8% of the participants who developed RFS received nasogastric tube feeding at some point before its development.

Conclusion: Nasogastric tube feeding and the presence of oedema may be possible risk factors for the development of RFS in patients with SAM, but larger samples need to be studied to inform the World Health Organisation (WHO) guidelines for the identification, management, and treatment of participants with SAM who are more likely to develop RFS.

Keywords: Refeeding syndrome, severe acute malnutrition, protein intake, energy intake, oedema

5.2 Introduction

The World Health Organisation continuously aims to improve the management guidelines of complicated SAM in order to reduce mortality rates related to malnutrition (Tickell & Denno, 2016:642). The WHO first published guidelines in 1981 to treat and manage severe protein-energy malnutrition (WHO, 1999:v). These were revised in 1999 as the treatment of severe acute malnutrition (SAM) (WHO, 1999:v), with a further revision in 2003 (Tickell & Denno, 2016:648). Another revision of the guidelines was issued in 2013 (Tickell & Denno, 2016:1). With these guidelines, the WHO (2013b:9) aims to reduce stunting by 40% and decrease wasting in children to less than 5% by 2025. Furthermore, the WHO indicates that mortality rates can drop below 10% by applying the WHO management guidelines to patients admitted with complicated SAM (Tickell & Denno, 2016:642). However, despite the implementation of these guidelines, mortality rates range from 12% to over 20% in African hospitals (Bhutta et al., 2017:13; Carboo et al., 2020). In addition, children with human immunodeficiency virus (HIV) admitted to hospital with SAM in sub-Saharan Africa are reported to have a threefold increased risk in mortality (Bhutta et al., 2017:13). With this in mind, a local study in KwaZulu-Natal investigating dietary practices for the treatment of SAM in a high HIV setting found that dietitians often followed their own professional opinion instead of the WHO protocol (Biggs, 2013:175).

Moreover, children with SAM are at risk of developing a complication known as refeeding syndrome (RFS) (Mbethe & Mda, 2017:1; Okinyi, 2018:69). Refeeding syndrome “is a metabolic condition characterised by severe electrolyte and fluid shifts in response to the transition from a catabolic to an anabolic state after start of nutritional therapy in malnourished patients” (Friedli et al., 2020a:2), and usually occurs within five days after the start of nutritional therapy (da Silva et al., 2020:189). Symptoms range from mild clinical signs and symptoms to severe and possibly fatal complications (Friedli et al., 2020a:2). A large randomised trial which included 967 participants admitted to Kantonsspital Aarau and University Hospital Bern in Switzerland, who were classified at nutritional risk and were likely to be admitted for more than five days, has shown that RFS worsens outcomes of patients, and is significantly associated with increased mortality (Friedli et al., 2020a:1; Friedli et al., 2020b:140).

To further complicate matters, the WHO dietary guidelines (Table 5.1) for the treatment of SAM differ from those developed to prevent refeeding syndrome in children, yet SAM has been identified as a significant risk factor for the development of RFS (da Silva *et al.*, 2020:12). The WHO guidelines seem to be effective in reducing the risk of RFS by slowly increasing energy when transitioning from the stabilisation to the rehabilitation phase, but it remains unclear whether this approach should be revised to improve outcomes (WHO, 2013b:40-41). Additionally, in the paediatric population, various sets of dietary guidelines have been developed to prevent RFS, and are summarised in Table 5.3. Of importance is the presence of bilateral pitting oedema because the WHO guidelines have different initial feeding volume requirements for children with severe oedema thereby providing less energy and protein. However, dietary requirements for RFS do not consider oedema. The dietary guidelines discussed in this article only focus on energy and protein in order to compare the intake of participants to the requirements of the WHO as well as the guidelines for RFS. Table 5.2 indicates the analysis of the stabilisation feed namely F-75 recommended by the WHO for the initial dietary treatment of complicated SAM. Correspondingly, authors have, cautioned against the use of F-75 substitutes as they do not improve clinical outcomes or reduce RFS in children admitted with SAM (Namusoke et al., 2016; Bandsma *et al.*, 2019:14-15).

Table 5.1: Summary of WHO dietary requirements for children with SAM between 6 – 59 months

Phase of feeding	Fluid		Energy (kcal/kg)		Protein (g/kg)	
	No oedema	+++[1] oedema	No oedema	+++ oedema	No oedema	+++[1] oedema
Stabilization	130 ml/kg F-75	100 ml/kg F-75	100	75[2]	1 – 1.5	0.9[2]
Transition	Change to equal volumes of F-100 for two days		100 – 135		Not specified	
Rehabilitation	On day three, increase F-100 by 10 ml for each consecutive feed until the child's appetite is satisfied.		150 – 220		4 – 6	

[1] "+ Mild: both feet; ++ moderate: both feet, plus lower legs, hands, or lower arms; +++ severe: generalized oedema including both feet, legs, hands, arms and face" (WHO, 2013b:4)

[2] Amount of energy and protein per kilogram that F-75 would provide according to the WHO prescription.

Table 5.2: F-75 ready to drink therapeutic feed: Typical nutritional information (Aspen Nutritionals, 2015)

Average analysis	Unit	Per 100ml	% Total energy
Energy	kcal	75	-
Protein	g	0.9	4.9
Carbohydrates	g	13	70.4
Fat	g	2	24.2
Magnesium	mg	10.5	-
Phosphorus	mg	24	-
Potassium	mg	157	-

Table 5.3: Paediatric dietary guidelines developed to prevent RFS

Author	Population	Criteria		Age (years)	Energy	Protein (g/kg)
Afzal *et al.* (2002)	RFS in children who received enteral nutrition	Periods of inadequate nutrition		< 7	80 –100 kcal/kg	▪ 0.6 – 1.0 ▪ Increase to 1.2 – 1.5 over three to five days
				7–10	75 kcal/kg	
				11–14	60 kcal/kg	
				15–18	50 kcal/kg	
		More severe cases (75% of requirements)		< 7	60 – 75 kcal/kg	
				7–10	56.3 kcal/kg	
				11–14	45 kcal/kg	
				15–18	37.5 kcal/kg	
O' Connor & Nicholls (2015)	Eating disorders	Primary phase	Day 1	Not specified	40 kcal/kg	Not specified
			Day 2		Increase by 200kcal/day	
		Secondary phase (Day 2 – 4)	Achieve adequate weight gain (0.5 – 1.0 kg/ week)		Basal metabolic rate (BMR) x physical activity level (PAL)	
			Once weight gain reduces		increase by 200 – 300 kcal/day	
		Tertiary phase (Day 7 – 14)	Maintain if adequate weight gain		Estimated average requirement energy for height age	
		Progression phase	If sufficient weight gain not achieved		Increase by 200 – 300 kcal/day every four days until weight gain of 0.5 – 1 kg/week	
		Maintenance phase	Once weight >85% median BMI		Slow or maintain weight gain according to therapeutic plan	
Meyer & Marino (2015)	Paediatric ICU patients at high risk of RFS	▪Acute illness ▪Inadequate nutrition >5 days	If: ▪ K <3.0 mmol/L ▪ PO_4 <0.65 mmol/L	0 – 1	70 – 80 kcal/kg	▪ Infants: 1 (Goal1.2 – 1.5 to 2.0 – 2.5)
				1 – 7	60 – 75 kcal/kg	

		▪Use of certain chronic medications, e.g. antacids, steroids, diuretics, diabetic	▪ Mg < 0.5 mmol/L	7–10 11–14 15–18	45 – 55 kcal/kg 45 kcal/kg 35 kcal/kg	▪ Children (1–7y): 0.6–1.0 (Goal: 1.2–1.5) ▪ Children (8–18y): 0.8 – 1.0 (Goal: 1.5)
da Silva et al. (2020)	Paediatric patients at risk of RFS	See da Silva et al. (2020:189) for detailed criteria		Not specified	40%–50% of goal (Starting the glucose infusion rate around 4–6 mg/kg/min and increasing by 1–2 mg/kg/min daily as blood glucose levels allow until you reach a max of 14–18 mg/kg/min. This includes enteral as well as parenteral glucose.)	Not specified

Overall the WHO feeding guidelines for the treatment of SAM improve patients' outcomes and are effective in reducing the risk of RFS (WHO, 2013b:41). However, mortality rates remain high in children admitted with SAM, especially those with HIV, despite the implementation of these guidelines (Bhutta et al., 2017:13; Carboo et al., 2020). Not only have studies shown that dietitians have inconsistent dietary practices for SAM and RFS (Wagstaff, 2011; Biggs, 2013), but there are also discrepancies in the dietary guidelines for the treatment of SAM and the prevention of RFS which may lead to further inconsistent dietary practices.

This study aimed to identify RFS in children admitted to Rahima Moosa Mother and Child Hospital, and determine dietary-related factors such as energy and protein intake, the WHO phase of feeding, type of feed, NGT feeding and presence of oedema, that may have been related to the development of the syndrome.

5.3 Methods

5.3.1 Study design, setting and study population

A retrospective analytical cohort study of retrievable hospital files and NCRs of children aged 0 – 59 months admitted with SAM to Rahima Moosa Mother and Child Hospital, Coronationville, Johannesburg, South Africa between 1 October 2014 – 31 December 2018, was conducted.

5.3.2 Ethical considerations

Ethical approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State. Permission was also obtained from the Gauteng Department of Health as well as the Chief Executive Officer of Rahima Moosa Mother and Child Hospital, to perform the study and retrieve retrospective information from hospital files between October 2014 to December 2018. All patients' data, as well as physicians and other medical professionals' information, were kept confidential.

5.3.3 Sampling

A total number of 592 children were admitted with SAM during the period under review, according to computerised statistics at the Dietetics Department. Of these, only 148 hospital files could be traced and retrieved. The researcher verified the diagnosis on each of these 148 files by applying the WHO criteria to information obtained from hospital files i.e. weight-for-length/height <-3 SD (using the WHO tables available online at https://www.who.int/childgrowth/standards/weight_for_length_height/en/), or MUAC <11.5 cm in children older than six months, or the presence of bilateral pitting oedema (WHO, 2013b:2). Twenty-two patients were excluded due to the incorrect classification of SAM on admission by doctors. 17 of these patients were MAM, two patients had mild malnutrition (weight-for-length/height above -2 SD), two patients had a normal weight-for-length/height and one patient was too old. Reasons for incorrect classifications were found to be incorrect anthropometry on admission and use of phone applications that not certified by the WHO. Only patients with confirmed SAM were eligible for inclusion in the study. The final sample comprised 126 participants, which represented only 21% of the children admitted with SAM during the period under review.

5.3.4 Data collection

Date of birth, age, gender, weight, length/height, MUAC presence of bilateral pitting oedema noted on admission by the physician, were recorded from the hospital files to confirm the diagnosis of SAM. Nutrition Care Records (NCRs), a dietetics document containing the nutritional prescription and management notes, archived in the dietetics department, were traced for those patients with confirmed SAM. To determine the incidence of RFS, phosphate blood values for the first two weeks of hospitalisation were recorded from the hospital files. Concerning the dietary prescription, energy and protein intake, WHO phase of feeding and the type of feed prescribed were recorded from the NCRs and/or hospital files. This information was noted for the first week, as RFS occurs mainly within the first two to five days after initial feeding (Crook, 2014:1452; Kerubo, 2017:39; Parli et al., 2014:197) and the initial stabilisation phase of feeding in the management of SAM could take between two and seven days before a patient is ready for rehabilitation (WHO, 1999:15). If RFS occurred after the first week, the dietary prescription was recorded until RFS occurred. The presence of oedema and the application of NGT feeding were also noted from hospital files on admission, and for the duration of hospital stay until RFS occurred in the RFS-positive participants.

5.3.5 Data analysis

The incidence of RFS in the sample was determined. Participants were divided into two groups, namely, the RFS-positive group i.e. those who developed RFS, and the RFS-negative group i.e. those who did not develop RFS. The onset of RFS was defined as a drop in phosphate by $\geq$0.16 mmol/L to a value $\leq$0.65 mmol/L. This definition by Marik & Bedigian was one of the more frequently used definitions at the time of the study (Marik & Bedigian, 1996:1044; Friedli et al., 2017:154). The recorded data was described in terms of medians and percentiles for numerical data, and frequencies and percentages for categorical data.

5.4 Results

Refeeding syndrome occurred in 8.7% (n=11) of participants admitted (n=126) with SAM. The total sample had a median age of 34.2 months (IQR: 22.4). The majority of participants were male (62.7%), African (95.2%) and from South Africa (64.3%) and Zimbabwe (21.4%). Concerning dietary intake, the median energy intake on day one of hospitalisation for the RFS-positive group was 69 kcal/kg (IQR: 22) compared to 83.5 kcal/kg (IQR: 22) in the RFS-negative group. Furthermore, the median protein intake on day one of hospitalisation in the RFS-positive group was 1.2 g/kg (IQR: 0.55) compared to 1.3 g/kg (IQR: 0.35) in the RFS-negative group. The dietary intake on day one of hospitalisation was, however, not significantly different between the two groups. The median energy and protein intake for the RFS-positive and negative groups during the first five days of hospitalisation is described in Table 5.4 and schematically represented in Figure 2 and Figure 3. The RFS-negative group had a significantly higher intake of energy on day four (p=0.04) and day five (p=0.001) of hospitalisation compared to the RFS-positive group. Protein intake was also significantly more in the RFS-negative group on day four (p=0.04) and day five (p=0.04) of hospitalisation compared to the RFS positive group.

Table 5.4: Median energy and protein intake for the first five days of hospitalisation stratified according to the development of RFS

	Median energy intake			Median protein intake		
Day	**RFS-positive group**	**RFS-negative group**	**P-value**	**RFS-positive group**	**RFS-negative group**	**P-value**
1	69	83.5	0.07	1.2	1.3	0.49
2	80	87	0.31	1.2	1.5	0.27
3	80	84.5	0.19	1.3	1.5	0.32
4	77	89	0.04*	1.3	1.5	0.04*
5	75	100	0.001*	1.5	1.6	0.04*

*p<0.05 was considered significant

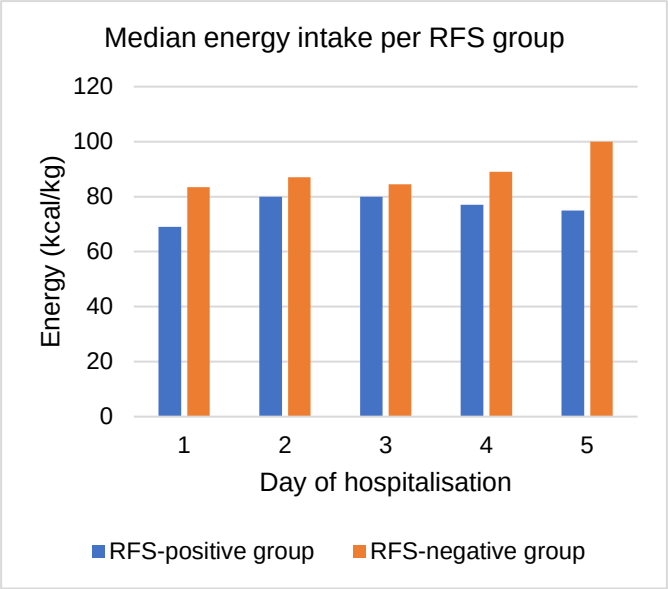

Figure 5.2: Median energy intake per RFS group

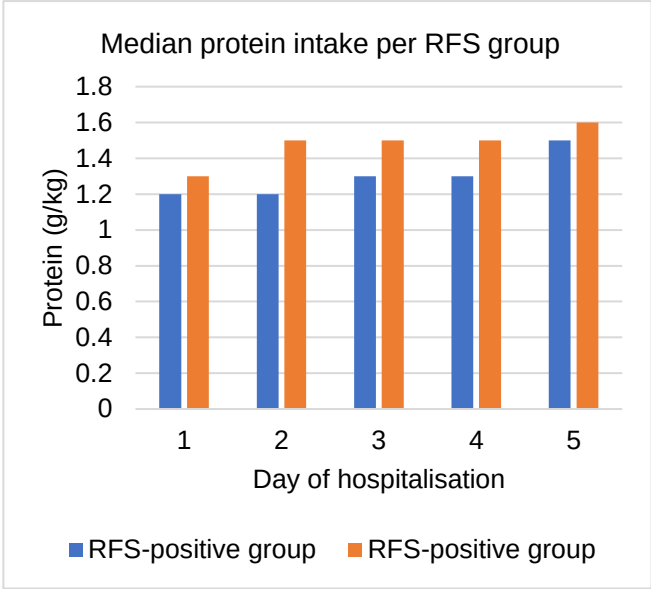

Figure 5.1: Median protein intake per RFS group

The median intake during the first five days for the RFS-positive group (n=11) was 77 kcal/kg compared to 87 kcal/kg in the RFS-negative group (n=115). The median protein intake during the first five days was 1.3 g/kg for the RFS-positive group compared to 1.5 g/kg in the RFS-negative group. Table 5.5 indicates the various formulas that were prescribed to participants in the RFS-positive and RFS-negative groups, respectively. The majority of participants in both groups received standard formula for the first five days of hospitalisation.

Table 5.5: Formulas prescribed during the first five days of hospitalisation stratified according to the development of RFS

Day	Number (%) of participants in the RFS-positive group				Number (%) of participants in the RFS-negative group			
	F-75	Standard	Soy	Hydrolysed	F-75	Standard	Soy	Hydrolysed
1	3 (27.3%)	6 (54.5%)	0	0	28 (24.3%)	44 (38.3%)	0	0
2	3 (27.3%)	6 (54.5%)	0	1 (9.1%)	14 (12.2%)	67 (58.3%)	2 (1.7%)	1 (0.9%)
3	3 (27.3%)	6 (54.5%)	1 (9.1%)	1 (9.1%)	0	59 (51.3%)	6 (5.2%)	6 (5.2%)
4	1 (9.1%)	7 (63.6%)	1 (9.1%)	2 (18.2%)	7 (6.1%)	60 (52.2%)	5 (4.3%)	9 (7.8%)
5	0	5 (45.5%)	1 (9.1%)	4 (36.4%)	5 (4.3%)	59 (51.3%)	5 (4.3%)	8 (7%)

Oedema was more prevalent on admission in participants who developed RFS (63.6%), compared to those who did not develop RFS (39.1%), but the difference was not statistically significant (p=0.2). Two participants, however, only developed oedema only on day three and day five of hospitalisation respectively, which was not included in the analysis on day one of hospitalisation. Thus, 81.8% of the participants had oedema when the diagnosis of RFS was made. NGTs were placed in 36.4% of participants in the RFS-positive group and 20.9% of participants in the RFS-negative group on admission, but the difference was not statistically significant between the groups (p=0.26). However, 81.8% of participants who developed RFS had NGTs placed either on admission or before the development of RFS. Neither the presence of oedema nor NGT placement after admission was recorded for the RFS-negative group and could, therefore, not be compared Table 5.4 summarises information of the RFS-positive group such as when the participants developed oedema, when NGTs were placed, the drop in phosphate blood levels from baseline, analysis of the dietary prescription on the day RFS was diagnosed and the type of formula that the participant was receiving. Of those that developed RFS, 64.5% received standard formula, 27.3% received hydrolysed formula and 9.1% received either soy or F-75 formula on the day RFS was diagnosed. With regard to the WHO phases of feeding, 90.9% of the participants were in the initial phase of feeding and only one patient was in the transition phase of feeding. The data showed that 45.5% of patients developed RFS within the first three to five days after initiating feeds and 54.5% developed RFS between day six and day thirteen.

Table 5.6: Summary of the dietary prescription analysis of the participants who developed RFS

Participant	Oedema	Day oedema recorded in the file	Day NGT placed	Day of RFS	Phosphate value (mmol/L)		Energy intake day of RFS (kcal/kg)	Protein intake day of RFS (g/kg)	Type of formula day of RFS
					Baseline	Day of RFS			
1	Yes	1	2	4	0.6	0.44	77	1.5	Standard
2	Yes	1	3	6	0.69	0.46	100	1.5	Standard
3	Yes	1	5	10	0.9	0.59	62	1.5	Hydrolysed
4	Yes	1	1	3	0.7	0.53	68	0.8	F-75
5	No	No oedema	1	3	1.16	0.65	49	1.0	Standard
6	Yes	1	1	6	1.03	0.47	90	1.3	Standard
7	Yes	1	2	9	1.2	0.59	61	1.5	Hydrolysed
8	No	No oedema	No NGT	4	0.9	0.31	100	1.5	Standard
9	Yes	1	No NGT	5	1.03	0.35	125	2.0	Standard
10	Yes	3	12	13	2.37	0.63	100	2.0	Hydrolysed
11	Yes	5	1	9	2.4	0.62	88	1.7	Soy infant

5.5 Discussion

In this study, refeeding syndrome occurred in 8.7% (n=126) of participants admitted with SAM. Participants in both the RFS-positive and RFS-negative groups had suboptimal median energy intakes, but adequate median protein intakes according to the requirements recommended by the WHO, for the first five days of hospitalisation. The majority of participants were identified as having been in the initial phase of dietary treatment when RFS occurred. On the day of RFS diagnosis, only one participant received F-75, in accordance with WHO guidelines, while the rest received either standard infant formula, soy infant formula or hydrolysed infant formula. Contrary to expectations, most participants who developed RFS did so after five days of initialising the feed. In addition, more than 80% of participants who developed RFS had an NGT placed on admission and had oedema when RFS was diagnosed.

Concerning energy and protein intake, the median energy for the first five days of hospitalisation was suboptimal in both the RFS-positive and negative groups, whereas protein intake was adequate when compared to the recommendations of the WHO requirements for the initial phase of the treatment of SAM which could take as long as two to seven days. The recommended energy and protein intake as per the WHO

requirements for initial phase feeding is 100 kcal/kg/day and 1 – 1.5 g/kg/day (WHO, 2013:209). However, for patients with SAM who present with severe oedema, the WHO recommends providing F-75 at 100 ml/kg which would provide an energy and protein intake of 75 kcal/kg/day and 0.9 g/kg/day respectively (WHO, 2013:209). In this study, oedema was present in 81.8% of the participants at the time of RFS diagnosis which could indicate that the energy prescription for the majority of the RFS-positive group was actually in line with the WHO recommendations, but that their protein prescriptions exceeded the WHO recommendation. The grade of oedema was, however, unfortunately not taken into consideration in this study, mainly because the grade of it was, unfortunately, not routinely recorded in the hospital files or NCRs. Furthermore, with only 39.1% of participants in the RFS-negative group having oedema, one may deduce that the majority of these participants had a median suboptimal energy intake, but adequate protein intake during the first five days of hospitalisation. A possible reason for this finding is the fact that F-75 was not used routinely at the time of the study, and that other infant formulas have lower energy content and higher protein content than F-75. Furthermore, The RFS-negative group had a significantly higher intake of energy and protein on day four and day five of hospitalisation compared to the RFS-positive group. An explanation for this could be that children in the RFS-positive group were clinically better and had less oedema to have provided them with more energy and protein compared to the RFS-negative group.

The median energy and protein intakes were also compared to the recommendations to prevent RFS as defined by Afzal et al.'s (2002) requirements, on day one of hospitalisation. This reference was chosen as the requirements are age-specific, have a similar population, and also include protein recommendations which are absent in other references. The median energy intake on day one for the RFS-positive group was in line with recommendations of Afzal et al. (2002) of 60 – 75 kcal/kg for more severe cases of malnutrition, and the RFS-negative group was in line with the recommendation of 80 – 100 kcal/kg for less severe cases of malnutrition. However, the median protein intake on day one for both groups exceeded the initial recommendation of 0.6 – 1 g/kg. In the participants with oedema, the amount of protein per kg of dry weight (oedema free weight) would then be even greater than the results indicated. Crook (2014:1453) has suggested that the feed composition may

be more important than the amount of energy the feed contains. Furthermore, Crook (2014:1453) also notes that hypophosphataemia is less likely to occur with lower protein intake. The presence of oedema and high protein intake could, therefore, be the confounding reason for the development of RFS, as oedema was more prevalent in the RFS-positive group.

As mentioned earlier, the WHO protocol for the treatment of SAM has incorporated an intermediate phase of feeding between the stabilisation and rehabilitation phases, namely the transition phase of feeding. During the transition phase, energy and protein intake are gradually increased which seems to be effective in decreasing the risk of developing RFS (WHO, 2013b:40-41). In this study, according to the RFS-positive participants' energy and protein intake, the majority of participants (90.9%) developed RFS during the stabilisation phase of feeding and one participant (9.1%) developed RFS in the transition phase of feeding. In terms of when RFS occurred in this study, 45.5% of the participants developed RFS within the first three to five days after initiating feeds and 54.5% developed RFS between day six and day thirteen. These findings are, therefore, not in keeping with one of the main characteristics of RFS that have thus far been established, namely the development of the syndrome within two to five days after initiating feeding (Araujo Castro and Vázquez Martínez, 2017:472; Mehanna et al., 2008:1495; Parli et al., 2014:197; Skipper, 2012:35). Furthermore, the majority of these participants were, therefore, in the stabilisation phase for longer than the standard period of more or less two to seven days, indicating that these participants were possibly more ill and had not presented with clinical signs (such as improved appetite) that would have allowed them to move to the transition phase of feeding at an earlier stage. Therefore, longer periods of stabilisation may be a risk factor that predisposes patients to develop RFS.

In this study, all participants admitted with SAM were treated according to the WHO 10-step protocol, but alternative formulas were used instead of F-75 as the latter was only available for use in the admission ward. Thereafter, formulae that were supplemented by the dietitians to reach WHO requirements were initiated after participants were admitted to the ward. Moreover, to meet the micronutrient and electrolyte requirements that would normally be provided by giving F-75, physicians prescribed electrolytes and micronutrients as per the WHO recommendations for

SAM. Thus, the micronutrient and electrolyte intake would be in accordance with the WHO guidelines whether the participant received F-75 or not. The majority of participants received standard formula during the first five days of hospitalisation. Furthermore, in the RFS-positive group of this study, 64.5% of participants received standard formula, 27.3% received hydrolysed formula and 9.1% received either soy or F-75 formula at the time of RFS diagnosis. Notably, Namusoke et al. (2016:557) have recommended using F-75 substitutes with caution, especially those with suboptimal mineral content. Therefore, F-75 appears to be a more effective treatment option than substitute formulae with individual electrolyte and micronutrient supplementation.

Lastly, NGT placement on admission was not found to be statistically significantly associated with RFS in this small sample. However, the majority of the RFS-positive group received NGT feeding at some point before RFS occurred which correlates to research that has shown that NGT feeding increases the risk of RFS (Afzal et al., 2002:515,516,519; Morton-Nance, 2013:20; Crook, 2014:1453; Bhutta et al., 2017:11) Furthermore, the WHO recommends NGT feeding in participants with SAM who consume less than 80 kcal/kg/day (WHO, 2013a:209) which could put patients at a greater risk of developing RFS. However, NGT placement after admission was only noted in the RFS-positive group, and therefore could not be compared to the RFS-negative group.

5.6 Limitations

Among the limitations of the study, the small sample must be emphasised, as it limited the power of the study and may have affected the results and the significance thereof. The small sample size was influenced by the inability to retrieve the necessary hospital files and NCRs due to misfiling and a lack of organisation. In addition, the researcher had to rely on the information recorded in the hospital files and NCRs completed by others. Thus, there was no way of knowing whether the data was consistently captured. Moreover, important information such as the grade of oedema to determine the adequacy of dietary intake compared to the WHO dietary requirements could not be determined as this was not routinely indicated in the hospital files. Lastly, not

having access to F-75 for the initial dietary treatment of participants after admission may have influenced the findings of this study.

5.7 Conclusion and recommendations

Dietary factors related to protein and energy intake were inconclusive due to the researcher's inability to determine the adequacy of intake against the WHO requirements of SAM, as the grade of oedema, which influences the nutritional requirements, was not routinely noted in the hospital files. The majority of participants developed RFS after day five of hospitalisation which is not consistent with the definition for RFS. In addition, the majority of participants who developed RFS received F-75 substitutes. Therefore, dietitians should follow the WHO guidelines and use F-75 substitutes during the stabilisation of children with SAM with caution. Lastly, the presence of oedema and high protein intake could be associated with the development of RFS but should be addressed with more research on larger samples.

This study highlighted the importance of determining the grade of oedema and recording this information in hospital files. Also, it is vital to medical personnel to identify, classify and capture grades of oedema to ensure the uniform management of patients. It is also very important not to exceed protein requirements, especially in patients with severe oedema. For institutions where F-75 is unavailable or out of stock, the guidelines for the management of SAM should also specify the protein and energy requirements for severe oedema (e.g. 75 kcal/kg and 0.9 g/kg protein), and not only state the recommended volume of F-75 per kilogram. Furthermore, F-75 substitutes should be used with caution due to their high protein content compared with F-75. Additional research on the impact of NGT feeding on the development of RFS could be beneficial in determining whether these patients require a more cautious feeding protocol compared to those who are not fed via NGT.

The small sample, which was the result of the inability to retrieve hospital files, highlights the importance of improving the filing and retrieval system of hospital files. This study also highlighted the importance of the correct classification of SAM. Improving the identification of SAM, through education on the correct methods of obtaining weight and length/height and use of the correct WHO resources to classify

children with SAM on admission can improve the accuracy of hospital statistics as well as provincial and national statistics of SAM.

In conclusion, the nutritional requirements for the prevention of RFS differ from the WHO guidelines for in-patient management of SAM. Additional studies with larger sample sizes are, therefore, needed to identify and confirm risk factors for RFS in SAM, in order to motivate for the incorporation of specific prevention and treatment guidelines for RFS in SAM management protocols.

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CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Introduction

This retrospective analytical cohort study yielded a sample of 126 participants aged 0 – 59 months who met the inclusion criteria of being diagnosed and verified with SAM from October 2014 to December 2018. The incidence of RFS was determined for the sample and data were compared between participants who developed RFS and those who did not develop RFS, to identify factors in SAM that may possibly be associated with the development of RFS.

In this final chapter, the limitations of the study and the impact thereof will be discussed. In addition, conclusions and recommendations from results of the study regarding the socio-demographic and clinical profiles, biochemistry, clinical signs and symptoms and the dietary prescription of participants are also discussed.

6.2 Limitations of the study

The small sample size was a significant limitation of this study. Whereas hospital statistical data indicated that 592 patients were admitted with SAM during the 5-year study period, only 148 of the records for these patients could be retrieved, mostly as a result of an inadequate filing system. Having relied on SAM checklists, which did not represent the total population of patients admitted with SAM to Rahima Moosa Mother and Child Hospital, also affected the sample size. Furthermore, the researcher was compelled to rely on data captured by others, thus, there was no way of knowing whether the data was consistently captured. Lastly, having to deviate from the WHO protocol due to not having access to F-75, may have influenced the findings of this study.

6.3 Conclusions and recommendations

Conclusions and recommendations are summarised in terms of the research objectives.

6.3.1 Socio-demographic and clinical profiles

Conclusion: The study sample, as well as participants in the RFS-positive and RFS-negative groups, were mostly male, of African descent and from South Africa and Zimbabwe. The male predominance in this study supports Svedberg's (1990:471) finding of a slightly higher prevalence of wasting in pre-school boys than in girls. The RFS-positive group were younger (9.4 months; IQR: 9.6) than the RFS-negative group (12.8 months; IQR: 12.8), although the difference was insignificant. The median stay in hospital was significantly longer for the RFS-positive group than in the RFS-negative group (p=0.003). The reason for this can possibly be explained by findings from Friedli et al.'s (2020a:1) randomised trial that found RFS to be associated with poorer clinical outcomes and a longer length of hospitalisation.

Furthermore, 15.1% (n=19/126) of the total sample demised of which two participants were in the RFS-positive group (18.2%). The hospital files of deceased patients were more easily obtained which could be attributed to the fact that these files were archived in a separate location by a different group of hospital clerks where a more rigid system of control was exercised. Therefore, by improving the storage and retrievability of hospital files is vital for the continued care of patients who are re-admitted to the hospital. To add, an improved archiving system of hospital files will ensure larger sample sizes for future retrospective studies.

Recommendations: Archiving hospital files of patients who are discharged from hospital needs to be improved. This can be done by implementing a more rigid control system by archiving files as soon as patients are discharged from hospital and implementing a file control sheet of issuing and receiving files. These are the control measures that are used for files of deceased patients at Rahima Moosa Mother and Child Hospital.

6.3.2 Anthropometry and clinical data to confirm the diagnosis of SAM

Conclusion: This study excluded 22 hospital files of patients who had been diagnosed with SAM, but where the researcher, by applying the WHO definition, found that the diagnosis was incorrect. Of these 22 patients (14.9%), 17 were MAM, two had mild malnutrition (weight-for-length/height >-2 SD), two had a normal weight-for-length/height and one was too old. These misdiagnoses occurred owing to the incorrect measurement of anthropometry and physicians and dietitians incorrectly interpreting weight and length/height against various growth standards. These participants were thus classified as SAM and reflected as SAM on the available statistics, but when the diagnoses were verified by the researcher, they were found to be incorrect. Carboo et al. (2020:3) have highlighted the lack of available information regarding the diagnosis and identification of children with SAM in African hospitals. They also discuss the controversial debate over the favoured tool to diagnose SAM and that MUAC and weight-for-length/height correlate poorly with one another when identifying children with malnutrition. Not only can the use of different tools for the diagnosis of SAM be a possible reason for different interpretations for SAM, but obtaining the correct weight and length/height is essential in order to interpret the available tools correctly. Use and interpretation of the correct tools are imperative not only to identify and treat patients with SAM appropriately but also to improve provincial, national and international statistics of SAM.

Furthermore, on admission, the RFS-positive group was younger, shorter and weighed less than the RFS-negative group. However, none of the anthropometrical indices was significantly different between the two groups. Moreover, the presence of bilateral pitting oedema, which is an independent clinical sign for the diagnosis of SAM was more prevalent in participants who developed RFS. The presence of oedema was not statistically significantly associated with the onset of RFS in this study, However, Mbethe & Mda (2017) found oedema to be significantly more prevalent in participants who developed RFS, with only 104 participants in their study. Therefore, a link cannot be ruled out without further research as the small sample size in this study may have skewed the results. Also, identifying and recording the grade of oedema in hospital files is vital as the presence of severe (+++) oedema affects the dietary requirements and management of these patients (WHO, 2013a:209; WHO, 2013b:4).

Recommendations: All health professionals including dietitians, nurses and doctors, dealing with the admission of children with SAM, need to attend training workshops on how to weigh and obtain length/height correctly as well as what WHO resources are available to correctly interpret anthropometry and diagnose SAM correctly. Equally important is to provide training to all health professionals treating patients with SAM on how to identify the grade of oedema in patients with SAM and record this information in hospital files.

6.3.3 Biochemistry

Conclusion: Hypophosphataemia was the biochemical marker used to diagnose RFS in this study. Of the sample, 11 (8.7%) participants developed RFS during hospitalisation after feeding was initiated, based on a commonly used definition at the time of data collection, namely a drop in blood phosphate levels by $\geq$ 0.16mmol/L to $\leq$ 0.65 mmol/L (Marik & Bedigian, 1996:1044; Friedli et al., 2017:153). The result was notably lower than in two other studies which also determined the incidence of RFS in children below five years admitted with SAM. The difference in incidences between these studies is because the researchers used different definitions with different biochemical cut off values to diagnose RFS. The reason for this is explained by the absence of a standardised definition for RFS and thus, the true incidence of RFS remains unknown (da Silva et al., 2020:179).

In addition, participants that developed RFS were significantly associated and more likely to present with hypophosphataemia (p=0.03), hypokalaemia (p=0.0005) and hyponatraemia (0.004) on admission. Studies have shown that electrolyte disturbances can result from malnutrition itself, sepsis, renal dysfunction and medication side effects, among others (Rady & Mohamed, 2014:4 Runde et al., 2019:166). Da Silva et al. (2020:11-12) have, however, identified decreased blood levels of phosphorus, potassium and magnesium before initiation of nutritional therapy as risk factors for developing RFS. The current WHO protocol for the management of SAM includes potassium and magnesium supplementation for all patients admitted with SAM. Brewster (2011:97) recommend that phosphate supplementation be added to the protocol for patients who are likely to develop. Additionally, although hyponatraemia normally occurs as a result of hyperglycaemia, which manifests during

RFS (Khan et al., 2011:2; Skipper, 2012:34), it has not yet been associated with the development of the syndrome.

Moreover, INR >1.7 on admission was significantly associated with RFS (p=0.049). An elevated INR is an indication of acute liver failure (Crismale & Friedman, 2020:655). International normalized ratio > 1.7 has been found to be significantly associated with increased mortality in children admitted with oedematous SAM (De Maayer and Saloojee, 2011:3). Studies have, however, not investigated INR as a possible risk factor for the development of RFS in SAM. A possible reason for the link between elevated INR and RFS may be attributed to the liver undergoing adaptations during starvation to preserve life. These adaptations include reduced gluconeogenesis and the production of transport proteins which consequently lead to liver dysfunction (WHO, 2004:35). INR may, therefore, be an important predictor of the severity of SAM and development of RFS, but more research in this regard will be beneficial.

Recommendations: The use of consensus definitions for RFS which have been recommended in recent publications (Friedli et al., 2020b:139; da Silva et al., 2020:189) could increase awareness of the syndrome as well as help to determine a more accurate incidence of RFS. In addition, a larger sample size and additional research into biochemical factors associated with the development of RFS in SAM may help with early identification of RFS and possibly motivate for a change in management for this sub-group of SAM patients. Furthermore, increased awareness of biochemical abnormalities on admission is vital as these abnormalities may not only be the result of malnutrition itself but may be involved in the development of RFS. As low levels of phosphate, potassium and magnesium have been identified as risk factors for the development of RFS, the addition of phosphate supplementation to the existing WHO protocol, which has also been recommended by Brewster (2011:97), could be beneficial in reducing the incidence of RFS.

6.3.4 Clinical signs and medical complications

Conclusion: The presence of UTI (p=0.04) and dehydration (p=0.03) on admission were significantly associated with the development of RFS in participants admitted with SAM. Urinary tract infection is commonly found in children with fever and is also more common in patients with SAM (Uwaezuoke, 2016:121). At the time of this study, however, the researcher could not find evidence on UTI associated with RFS.

Furthermore, dehydration on admission was significantly associated with the RFS (p=03). Dehydration may result from AGE and often occurs concurrently with SAM (Mwangome *et al.*, 2011:1). In this study, diarrhoea on admission showed a trend of being significantly associated with RFS and had there been a bigger sample, the association may have reached significance. Dehydration is also one of the many manifestations resulting from the fluid imbalances caused by RFS (Crook et al., 2001:633). Moreover, diarrhoea, which normally leads to dehydration, has also been associated with hyponatraemia, which was a significant finding in the RFS-positive group on admission, in children with SAM (Mwangome et al., 2011:1; Zogg et al., 2013:400). Additionally, Manary et al., (1998:790) found a significant correlation between dehydration and severe hypophosphataemia, whereas Kimutai et al., (2009:331) did not find dehydration to be significantly associated with RFS. The fact that there are conflicting results, more evidence is needed to confirm this finding.

Human immunodeficiency virus has been found to be significantly associated with RFS (Okinyi, 2018:69,71) as well as with increased mortality in patients with SAM (De Maayer and Saloojee, 2011:1,3). However, in this study, HIV was not significantly associated with RFS. A possible reason for not finding an association could be due to the small sample size, or alternatively due to the early initiation and adherence of antiretroviral drugs and better management of children with HIV over time. However, HIV-exposure and the onset of RFS was borderline significant (p=0.05). This association which could be related to other studies that have linked HIV-exposure to increased rates of death, infectious illness, as well as poor growth in infants (Evans et al., 2016:e92).

Recommendations: A larger sample and additional research into various clinical signs and symptoms on admission that could possibly identify patients who are at risk of developing RFS would be beneficial in motivating for a change in the management for these patients.

6.3.5 Dietary prescription analysis

Conclusion: In this study, protein and energy intake were inconclusive owing to the grade of oedema not being recorded in hospital files and NCRs which influences analysing and comparing intake to the WHO requirements as severe oedema affects the prescription. However, high protein intake in SAM participants with oedema on admission could possibly be associated with the development of RFS, but more research is required to confirm this finding. One reason for this could be due to the use of F-75 substitutes, which are normally lower in energy and higher in protein. The reason for using F-75 substitutes was mainly due to the lack of access to F-75 at the time of the study, and also due to medical complications that may have arisen in patients with SAM, such as malabsorption, protein-losing enteropathy and lactose intolerance which require careful assessment and consideration before deviating from the WHO protocol. Furthermore, of concern is that a South African study has found dietetic practices in the management of SAM to be based on personal expert opinion instead of the WHO protocol (Biggs, 2013:175). These finding further motivate the need for additional research in the field of SAM in order to address the many concerns that dietitians may have when treating patients with SAM which may cause them to deviate from the WHO protocol.

Contrary to the usual timing of the development of RFS, namely within two to five days after initiation of feeds, the majority of participants in this study developed RFS after day five of hospitalisation. Possible reasons for this could be the late insertion of NGTs and possibly the severity of SAM confounded by additional medical complications.

Recommendations: Additional research, on larger samples, into the safety of F-75 substitutes may motivate for additional funding from government and access to F-75 for all patients diagnosed with SAM in all institutions. Further research on the impact of NGT feeding on the development of RFS may be beneficial in determining whether children fed via NGT require a more careful and graded feeding approach compared to those who are able to feed orally.

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APPENDICES

Appendix A: Protocol and emergency treatment for the in-patient management of severely malnourished children

(WHO, 2009:43-44)

PROTOCOL FOR THE IN-PATIENT MANAGEMENT OF SEVERELY MALNOURISHED CHILDREN			
STEP	**PREVENTION**	**WARNING SIGNS**	**IMMEDIATE ACTION**
1. Treat or prevent Hypoglycemia *(Low blood sugar)* Hypoglycemia is a blood glucose <3mmol/L	For all children:- 1. Feed straightaway and then every 2-3 hours, day and night. 2. Encourage mothers to watch for any deterioration, help feed and keep child warm.	1. Low temperature (hypothermia) noted on routine check. 2. Lethargy, limpness and loss of consciousness. 3. Child can becomes drowsy.	Perform Dextrostix test on admission, before giving glucose or feeding. **If hypoglycemia is suspected and no dextrostix are available or if it is not possible to get enough blood for test, assume that the child has hypoglycemia and give treatment immediately without laboratory confirmation.** **If conscious:** 1. Give a bolus of 10% glucose (50ml) or sugar solution (1 rounded teaspoon sugar in 3 tablespoons of water). Bolus of 10% glucose is best, but give sugar solution or F75 formula rather than wait for glucose. 2. Start feeding straightaway: Feed 2-hourly (12 feeds in 24 hours). Use feed chart to find amount to give and feed every 2-3 hours day and night. **If unconscious,** give glucose IV (5ml/kg of sterile 10% glucose), followed by 50 ml of 10% glucose or sucrose by NG tube.
2. Treat or prevent Hypothermia *(Low temperature)* Hypothermia is a rectal temperature <35.5°C (95.9°F) or an underarm temperature <35°C (95°F).	For all children:- 1 Feed straightaway and then every 2-3 hours, day and night. 2. Keep warm. 3. Use the kangaroo technique, cover with a blanket. Let mother sleep with child to keep child warm. 3. Keep room warm, no draughts. 4. Keep bedding/clothes dry. Dry carefully after bathing (do not bathe if very ill). 5. Avoid exposure during examinations, bathing. 6. Use a heater or incandescent lamp with caution, **do not use** hot bottle water or fluorescent lamp.	Low temperature NOTE: Hypothermia in malnourished children often indicates coexisting hypoglycemia and serious infection.	Take rectal temperature on admission. (Ensure thermometer is well shaken down). **If the rectal temperature is below 35.5°C**: 1. Feed straightaway (or start rehydration if needed). 2. Re-warm. Put the child on the mother's bare chest (skin to skin contact) and cover them, OR clothe the child including the head, cover with a warmed blanket and place a heater or lamp nearby. 3. Feed 2-hourly (12 feeds in 24 hours). **Monitor during re-warming** • Take rectal temperature every two hours: stop re-warming when it rises above 36.5°C • Take every 30 minutes if heater is used because the child may become overheated.
3. Treat or prevent dehydration *(Too little fluid in the body)*	When a child has watery diarrhoea, give ReSoMal between feeds after each loose stool. As a guide, give 50-100ml after each watery stool if child is aged <2 years, or 100-200ml if aged 2 years or older.	Profuse watery diarrhoea, thirst, hypothermia, sunken eyes, weak or absent radial pulse, cold hands and feet, reduced urine output.	DO NOT GIVE IV FLUIDS EXCEPT IN SHOCK (see separate protocol for treating shock) **If dehydrated:** 1. Give ReSoMal 5ml/kg every 30 minutes for 2 hours (orally or by nasogastric tube) 2. Then give 5-10ml/kg in alternate hours for up to 10 hours (i.e. give ReSoMal and F75 formula in alternate hours). Use Initial Management Chart. 3. Stop ReSoMal when there are 3 or more hydration signs, or signs of over-hydration. **Monitor during rehydration for signs of over-hydration:** • increasing pulse and respiratory rate • increasing oedema and puffy eyelids Check for signs at least hourly. Stop if pulse increases by 25 beats/minute and respiratory rate by 5 breaths/minute.
4. Correct electrolyte imbalance *(Too little potassium and magnesium, and too much sodium)*	1. Use ReSoMal and F75 formula as these are low in sodium. 2. Do not add salt to food introduced during the rehabilitation phase.	Oedema develops or worsens.	**Follow feeding recommendation, as well as recommendation or prevention or treatment of dehydration:** Extra potassium (4mmol/kg body weight) and magnesium (0.6mmol/kg) are important. **For potassium**, add CMV or electrolyte/mineral solution or 10% potassium chloride solution to feeds and to prepare ReSoMal. If these are unavailable, give crushed Slow K ½ tablet/kg body weight daily. **For magnesium**, add CMV or electrolyte/mineral solution to feeds and to ReSoMal. NOTE: Potassium and magnesium are already added in ready to dilute F75 and F100 packets.

5. Treat infections	1. Keep malnutrition ward in a separate room 2. Reduce overcrowding if possible. 3. Wash hands before preparing feeds and before and after dealing with any child. 4.Give measles vaccine to unimmunized children over 6 months of age. 5. Good nursing care	NOTE: The usual signs of infection, such as fever, are often absent so **assume all** severely malnourished children have infection and treat with antibiotics. Hypothermia and hypoglycaemia are signs of severe infection. NOTE: ensure all doses are given. Give them on time.	**Starting on the first day, give broad-spectrum antibiotics* to all children.** 1. **If the child has no complications,** give:- Cotrimoxazole 5 ml paediatric suspension orally twice a day for 5 days **OR** 2. **If the child is severely ill** (apathetic, lethargic) or has complications (hypoglycemia, hypothermia, raw skin/fissures, respiratory tract or urinary tract infection) give IV/IM ampicillin AND gentamicin. • Ampicillin: 50mg/kg IM/IV 6-hourly for 2 days, then oral amoxycillin 15mg/kg 8-hourly for 5 days or if amoxycillin is not available continue with ampicillin but give orally, 50mg/kg 6-hourly • Gentamicin: 7.5mg/kg IM/IV once daily for 7 days. In addition, give Metronidazole according to national policy. **If a child fails to improve after 48 hours** ADD chloramphenicol 25mg/kg 8 hourly IM/IV for 5 day. **** Should be in line with national policy.*** **For parasitic worms (helminthiasis, whipworm)**: treatment should be delayed until the rehabilitation phase. For children over 2 years: Give Albendazole (400 mg, single dose) and Mebendazole 100mg orally twice a day for three days. For children under 2 years: Give pyrantel (10 mg/kg, single dose) or ascariasis with pyrantel or piperazine.
STEP	**MANAGEMENT**		
6. Correct micronutrient deficiencies	1. **Give Vitamin A on day 1**. If under 6 months give 50,000 units; if 6-12 months give 100,000 units; and if >12 months give 200,000 units. If the child has any signs of vitamin A deficiency, repeat this dose on day 2 and day 14. **Give the following daily**: 2. Folic acid : 5mg on day 1; then 1 mg daily if micronutrients not included in the feeds. 3. Multivitamin syrup 5 ml only if micronutrients not included in the feeds. 4. Zinc (2mg/kg body weight) and copper (0.3mg/kg body weight) if micronutrients not included in the feeds 5. Start iron (3mg/kg/day) after 2 days on F100 catch-up formula. **(Do not give iron in the stabilisation phase and do not give iron if child receiving RUTF)** NOTE: Vitamin A, folic acid, multivitamins, zinc and copper are already added in F75 and F100 packets. They are also in CMV.		
7. Begin cautious feeding stabilisation phase and transition phase	**Stabilisation phase:** 1. Give F75 formula (see feed chart for amounts). These provide 130ml/kg/day. 2. Give 8-12 feeds over 24 hours 3. If the child has oedema +++, reduce the volume to 100 ml/kg/day (see feed chart for amounts) 4. If the child has poor appetite, encourage the mother to coax and support the child finishing the feed. If eating 80% or less of the amount offered for 2 consecutive feeds, use a nasogastric tube. If in doubt, see feed chart for intakes below which tube feeding is needed. 5. Keep a 24-hour intake chart. Measure feeds carefully. Record leftovers. 6. If the child is breastfed, encourage continued breastfeeding but also give F75. 7. Transfer to F100 formula as soon as appetite has returned (usually within one week) and oedema has been lost or is reduced 8. Weigh daily and plot weight. **Transition phase:** 1. Change to F100: • for 2 days, replace F75 with the same amount of F100 on the next day increase each feed by 10ml until some feed remains uneaten.		
8. Increase feeding to recover weight loss: "Catch-up growth" rehabilitation phase	1. Give 6 feeds over 24 hours. These can be 3 feeds of F100 and 3 specially modified family meals, high in energy and protein. Ready-to-use therapeutic food is an alternative to F100, recommended to be given if the child is being referred to outpatient care. 2. Encourage the child to eat as much as possible, so the child can gain weight rapidly. If the child is finishing everything, offer more and increase subsequent feeds. Make sure that the child is actively fed. 3. Weigh daily and plot weight.		
9. Stimulate emotional and sensorial development: Loving care, play and stimulation	1. Provide tender loving care 2. Help and encourage mothers to comfort, feed, and play with their children 3. Give structured play when the child is well enough.		
10. Prepare for discharge and follow-up.	1. Obtain information on family background and socio-economic status. 2. Instruct mothers how to modify family foods, how often to feed and how much to give. 3. Establish a link with community health workers for home follow-up. 4. Write full clinical summary in patient-held card. 5. Send a referral letter to the clinic. 6. If outpatient management of severe malnutrition exists, inform the mother of the closest outpatient care referral point to her home and give the mother a weekly ration of RUTF for home based rehabilitation.		

EMERGENCY TREATMENT OF SEVERELY MALNOURISHED CHILDREN *Severely malnourished children are **different** from other children. So they need **different treatment.***	
CONDITION	**IMMEDIATE ACTION**
Treat shock Shock is if the child is lethargic **or** unconscious and cold hands **Plus either:** Slow capillary refill (longer than 3 seconds) **or** Weak fast pulse Monitor closely: use the Critical Care Pathway Initial Management Chart	**If child is in shock:** 1. Give oxygen 2. Give sterile 10% glucose (5ml/kg) by IV 3. Give IV fluid at 15ml/kg over 1 hour, using one of the following solutions in order of preference: • half-strength Darrow's solution with 5% glucose (or dextrose) • Ringers' lactate with 5% glucose* or • half-normal saline with 5% glucose* or **if either of these is used, add sterile potassium chloride (20 mmol/l) if possible.* 4. Keep the child warm. 5. Measure and record pulse and respirations every 10 minutes **If there are signs of improvement** (pulse and respiration rates fall) repeat IV 15ml/kg for one more hour **If there are no signs of improvement after the 1st hour of IV fluid** assume child has septic shock. In this case: 1. Give maintenance fluids (4ml/kg/h) while waiting for blood 2. Order 10ml/kg fresh whole blood and when blood is available, stop oral intake and IV fluids 3. Give a diuretic 4. Transfuse whole fresh blood (10ml/kg slowly over 3 hours) If signs of heart failure: give packed cells instead of whole blood.
Treat severe dehydration Assume severe dehydration if there is history of watery diarrhoea, thirst, hypothermia, sunken eyes, weakness or absent radial pulse, cold hands and feet, reduced urine output.	**DO NOT GIVE IV FLUIDS EXCEPT IN SHOCK** 1. Give ReSoMal 5ml/kg every 30min for 2 hours (orally or by NG). Do not give standard ORS to severely malnourished children 2. Measure and record pulse and respirations every 30 minutes. 3. Give ReSoMal 5-10 ml/kg/hour for next 4-10 hours in alternate hours with F75. **STOP** rehydration if 3 or more signs of rehydration or any signs of overhydration (increased respiratory rate and pulse rate, increase oedema and puffy eyelids). Only give ReSoMal for **up to 10 hours.** **Monitor during rehydration for signs of over-hydration:** • increasing pulse and respiratory rate • increasing oedema and puffy eyelids Check for signs at least hourly. Stop if pulse increases by 25 beats/minute and respiratory rate by 5 breaths/minute.
Treat very severe anaemia Very severe anaemia is Hb less than 4g/dl	**If very severe anaemia** (or Hb 4-6g/dl AND respiratory distress): 1. Stop all oral intake and IV fluids during the transfusion 2. Look for signs of congestive failure 3. Give furosemide 1ml/kg IV at the start of the transfusion 4. If no signs of congestive failure, give whole fresh blood 10ml/kg body weight slowly over 3 hours. If signs of heart failure, give 5-7ml/kg packed cells rather than whole blood.
Treat hypoglycaemia Hypoglycaemia is a blood glucose <3mmol/L Assume hypoglycaemia if no dextrostix available	Perform Dextrostix test on admission, before giving glucose or feeding. **If hypoglycemia is suspected and no dextrostix are available or if it is not possible to get enough blood for test, assume that the child has hypoglycemia and give treatment immediately without laboratory confirmation.** **If conscious:** 1. Give a bolus of 10% glucose (50ml) or sugar solution (1 rounded teaspoon sugar in 3 tablespoons of water). Bolus of 10% glucose is best, but give sugar solution or F75 formula rather than wait for glucose. 2. Start feeding straightaway: Feed 2-hourly (12 feeds in 24 hours). Use feed chart to find amount to give and feed every 2-3 hours day and night. If unconscious, **give glucose IV (5ml/kg of sterile 10% glucose), followed by 50 ml of 10% glucose or sucrose by NG tube.**
Treat hypothermia Hypothermia is a rectal temperature <35.5ºC (95.9ºF) or an underarm temperature <35ºC (95ºF).	**If hypothermia:** For all children: 1 Feed straightaway and then every 2-3 hours, day and night. 2. Keep warm. 3. Use the kangaroo technique, cover with a blanket. Let mother sleep with child to keep child warm. 3. Keep room warm, no draughts. 4. Keep bedding/clothes dry. Dry carefully after bathing (do not bathe if very ill). 5. Avoid exposure during examinations, bathing. 6. Use a heater or incandescent lamp with caution, **do not use** hot bottle water or fluorescent lamp.
Emergency Eye Care Corneal Ulceration	**If corneal ulceration:** 1. Give Vitamin A immediately (<6 months 50,000IU, 6-12 months 100,000 IU, >12 months 200,000IU) 2. Instil one drop atropine (1%) into affected eye to relax the eye and prevent the lens from pushing out.

Appendix B: Health Sciences Research Ethics Committee approval

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

11-Feb-2019

Dear **Miss Natalie Fourie**

Ethics Clearance: **The incidence of hypophosphataemia and associated factors related to refeeding in children aged 0 – 59 months diagnosed with severe acute malnutrition (SAM)**

Principal Investigator: **Miss Natalie Fourie**

Department: **Human Nutrition Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/0154/2602**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

Appendix C: Department of Health (NHRD) and Rahima Moosa Mother and Child Hospital approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

RAHIMA MOOSA MOTHER AND CHILD HOSPITAL

Enquiries : Karen Marshall
Tel : (011) 470 9284
Fax : (086) 553 4623

Department of Nutrition and Dietetics
University of the Free State

Dear Ms. Fourie,

RE: THE INCIDENCE OF HYPOPHOSPHATAEMIA AND ASSOCIATED FACTORS RELATED TO RE–FEEDING IN CHILDREN AGED 0 – 59 MONTHS DIAGNOSED WITH SEVERE ACUTE MAL–NUTRITION (SAM)

The Department of Health (NHRD ref no. GP_201806_028) and Rahima Moosa Mother and Child Hospital has granted you permission to conduct the research as indicated in the title above.

The terms under which this permission is granted is contained in the Researcher Declaration form that you have signed. Failure to comply with these conditions will result in the withdrawal of such permission.

It is crucial for you to inform the Research Coordinator, Karen Marshall of the actual start and end dates of your study. This could be done by e-mail.

Should the study commence more than 12 months after receipt of this approval letter you will have to go through the process of applying again.

You are strongly advised to keep a signed copy of the declaration form so as to ensure that the terms of this agreement are complied with at all times.

Yours sincerely,

DR FREW BENSON
Clinical Executive
2019:02:03

ADDRESS: CNR FUEL & OUDSTHOORN STREET CORONATIONVILLE 2093 / PRIVATE BAG X20 NEWCLARE 2112 JHB

Appendix D: Data Sheet

DATA SHEET - GENERAL INFORMATION						For office use only
Mark the appropriate block with a X or write the answer on the space provided.						
Respondent number:						Number
Date of data collection (dd/mm/yy):						Date of collection
Section A - Patient profile						**Section A**
1. Date of birth/DOB (dd/mm/yy):						1
2. Age (m):						2
3. Gender:	Male (1)	Female(2)				3
4. Country of origin:						4
5. Ethnicity:	White (1)	African (2)	Coloured (3)	Indian (4)		5
6. Date of admission (dd/mm/yy):						6
7. Date of discharge (dd/mm/yy):						7
8. Date of death (dd/mm/yy):						8
9. NCR available	Yes (1)	No (2)				9
Section B - Anthropometry						**Section B**
1. Weight on admission (kg):						1
2. Length/height on admission (cm):						2
3. MUAC on admission (cm):						3
4. Length/height re-taken by dietitian?	Yes (1)	No (2)				4
4.1 If yes - length/height (cm):						4.1
5. SAM diagnosed correctly?	Yes (1)	No (2)				5
6. Diagnosis based on:	6.1 Wt-lg/ht <-3SD	OR	Yes (1)	No (2)		6.1
	6.2 MUAC < 11.5cm	OR	Yes (1)	No (2)		6.2
	6.3 Bilat. pitting oedema		Yes (1)	No (2)		6.3
7. Include in study:	Yes (1)	No (2)				7
8. Weight on discharge (kg):						8
9. MUAC on discharge (cm):						9

DAILY DATA SHEET

Section C - Biochimistry

Respondent number: _____

	Biochemical value													
Day of hospitalisation:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
c1. Hb														
c2. Platelet count														
c3. CRP														
c4. Na														
c5. K														
c6. Urea														
c7. Creat														
c8. TBIL														
c9. ALP														
c10. GGT														
c11. ALT														
c12. AST														
c13. Alb														
c14. Ca														
c15. Mg														
c16. PO4														
c17. INR														

DATA SHEET

Section D - Clinical signs and medical complications

Respondent number: _____

Presense of clinical sign / medical complication [Indicate: Yes (1) / No (2)]					
Day of hospitalisation:	**1**				
d1. Vomiting					
d2. Diarrhoea					
d3. AGE					
d4. Dehydration					
d5. Bilat. pitting oedema					
d6. Dermatosis					
d7. Hypoglycaemia (<3)					
d8. Hyperglycaemia (>7)					
d9. Hypothermia (<35)					
d10. Pneumonia					
d11. Respiratory compl.					
d12. Sepsis					
d13. Septic shock					
d14. Loss of appetite					
d15. NGT					
d16. Hepatomegaly					
d17. Oral thrush					
d18. HIV +					
d19. HIV exposed					
d20. TB					
d21. UTI					
d22. Note (other):					

DAILY DATA SHEET

Section E - Dietary intake

Respondent number: __________

Mark the appropriate answer with a X or write the answer on the space provided.

Day: _____ (A) Phase (mark with an X): Stabilisation (1) Transition (2) Rehabilitation (3)			
(B) Weight (kg): _________	Energy (kcal)	Protein (g)	(E) Type of feed (mark with an X):
			e.1 F75: Yes (1)
			e.2 Standard formula: Yes (1)
			e.3 Soy formula: Yes (1)
	kcal/kg (C)	g/kg (D)	e.4 Hydrolysed formula: Yes (1)

Day: _____ (A) Phase (mark with an X): Stabilisation (1) Transition (2) Rehabilitation (3)			
(B) Weight (kg): _________	Energy (kcal)	Protein (g)	(E) Type of feed (mark with an X):
			e.1 F75: Yes (1)
			e.2 Standard formula: Yes (1)
			e.3 Soy formula: Yes (1)
	kcal/kg (C)	g/kg (D)	e.4 Hydrolysed formula: Yes (1)

Day: _____ (A) Phase (mark with an X): Stabilisation (1) Transition (2) Rehabilitation (3)			
(B) Weight (kg): _________	Energy (kcal)	Protein (g)	(E) Type of feed (mark with an X):
			e.1 F75: Yes (1)
			e.2 Standard formula: Yes (1)
			e.3 Soy formula: Yes (1)
	kcal/kg (C)	g/kg (D)	e.4 Hydrolysed formula: Yes (1)

Day: _____ (A) Phase (mark with an X): Stabilisation (1) Transition (2) Rehabilitation (3)			
(B) Weight (kg): _________	Energy (kcal)	Protein (g)	(E) Type of feed (mark with an X):
			e.1 F75: Yes (1)
			e.2 Standard formula: Yes (1)
			e.3 Soy formula: Yes (1)
	kcal/kg (C)	g/kg (D)	e.4 Hydrolysed formula: Yes (1)

Day: _____ (A) Phase (mark with an X): Stabilisation (1) Transition (2) Rehabilitation (3)			
(B) Weight (kg): _________	Energy (kcal)	Protein (g)	(E) Type of feed (mark with an X):
			e.1 F75: Yes (1)
			e.2 Standard formula: Yes (1)
			e.3 Soy formula: Yes (1)
	kcal/kg (C)	g/kg (D)	e.4 Hydrolysed formula: Yes (1)

For office use only

Respondent number: __________

Day: ________		A	E (Mark with an X)
		B	e.1 F75: Yes (1)
		C	e.2 Standard formula: Yes (1)
		D	e.3 Soy formula: Yes (1)
			e.4 Hydrolysed formula: Yes (1)

Day: ________		A	E (Mark with an X)
		B	e.1 F75: Yes (1)
		C	e.2 Standard formula: Yes (1)
		D	e.3 Soy formula: Yes (1)
			e.4 Hydrolysed formula: Yes (1)

Day: ________		A	E (Mark with an X)
		B	e.1 F75: Yes (1)
		C	e.2 Standard formula: Yes (1)
		D	e.3 Soy formula: Yes (1)
			e.4 Hydrolysed formula: Yes (1)

Day: ________		A	E (Mark with an X)
		B	e.1 F75: Yes (1)
		C	e.2 Standard formula: Yes (1)
		D	e.3 Soy formula: Yes (1)
			e.4 Hydrolysed formula: Yes (1)

Day: ________		A	E (Mark with an X)
		B	e.1 F75: Yes (1)
		C	e.2 Standard formula: Yes (1)
		D	e.3 Soy formula: Yes (1)
			e.4 Hydrolysed formula: Yes (1)

Appendix E: Subsequent Health Sciences Research Ethics Committee approval letters

UNIVERSITY OF THE FREE STATE
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YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

10-Jun-2019

Dear **Miss Natalie Fourie**

Ethics Number: UFS-HSD2018/0154/2602

Ethics Clearance: **The incidence of hypophosphataemia and associated factors related to refeeding in children aged 0 – 59 months diagnosed with severe acute malnutrition (SAM)**

Principal Investigator: **Miss Natalie Fourie**

Department: **Human Nutrition Department (Bloemfontein Campus)**

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

-Minor amendment

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
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UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

04-Sep-2019

Dear **Miss Natalie Fourie**

Ethics Number: UFS-HSD2018/0154/2602

Ethics Clearance: **The incidence of hypophosphataemia and associated factors related to refeeding in children aged 0 – 59 months diagnosed with severe acute malnutrition (SAM)**

Principal Investigator: **Miss Natalie Fourie**

Department: **Human Nutrition Department (Bloemfontein Campus)**

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

Minor amendment: Minor changes made to Protocol

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
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UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

20-Feb-2020

Dear **Miss Natalie Fourie**

Ethics Number: UFS-HSD2018/0154/2602

Ethics Clearance: **Refeeding syndrome characterised by hypophosphataemia in children aged 0 - 59 months diagnosed with severe acute malnutrition in a South African setting**

Principal Investigator: **Miss Natalie Fourie**

Department: **Human Nutrition Department (Bloemfontein Campus)**

SUBSEQUENT SUBMISSION APPROVED

With reference to your recent submission for ethical clearance from the Health Sciences Research Ethics Committee. I am pleased to inform you on behalf of the HSREC that you have been granted ethical clearance for your request as stipulated below:

Minor Amendment:
* Title amended from "The incidence of hypophosphataemia and associated factors related to refeeding in children aged 0 - 59 months diagnosed with severe acute malnutrition (SAM)" to "Refeeding syndrome characterised by hypophosphataemia in children aged
0 - 59 months diagnosed with severe acute malnutrition in a South African setting"

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this request for ethical clearance and we wish you continued success with your research.

Yours Sincerely

Dr. SM Le Grange
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Length	L	M	S	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2	SD3
45	-0.3833	2.4607	0.09029	1.9	2.1	2.3	2.5	2.7	3.0	3.3
45.5	-0.3833	2.5457	0.09033	2.0	2.1	2.3	2.5	2.8	3.1	3.4
46	-0.3833	2.6306	0.09037	2.0	2.2	2.4	2.6	2.9	3.2	3.5
46.5	-0.3833	2.7155	0.09040	2.1	2.3	2.5	2.7	3.0	3.3	3.6
47	-0.3833	2.8007	0.09044	2.2	2.4	2.6	2.8	3.1	3.4	3.7
47.5	-0.3833	2.8867	0.09048	2.2	2.4	2.6	2.9	3.2	3.5	3.8
48	-0.3833	2.9741	0.09052	2.3	2.5	2.7	3.0	3.3	3.6	4.0
48.5	-0.3833	3.0636	0.09056	2.4	2.6	2.8	3.1	3.4	3.7	4.1
49	-0.3833	3.1560	0.09060	2.4	2.6	2.9	3.2	3.5	3.8	4.2
49.5	-0.3833	3.2520	0.09064	2.5	2.7	3.0	3.3	3.6	3.9	4.3
50	-0.3833	3.3518	0.09068	2.6	2.8	3.1	3.4	3.7	4.0	4.5
50.5	-0.3833	3.4557	0.09072	2.7	2.9	3.2	3.5	3.8	4.2	4.6
51	-0.3833	3.5636	0.09076	2.8	3.0	3.3	3.6	3.9	4.3	4.8
51.5	-0.3833	3.6754	0.09080	2.8	3.1	3.4	3.7	4.0	4.4	4.9
52	-0.3833	3.7911	0.09085	2.9	3.2	3.5	3.8	4.2	4.6	5.1
52.5	-0.3833	3.9105	0.09089	3.0	3.3	3.6	3.9	4.3	4.7	5.2
53	-0.3833	4.0332	0.09093	3.1	3.4	3.7	4.0	4.4	4.9	5.4
53.5	-0.3833	4.1591	0.09098	3.2	3.5	3.8	4.2	4.6	5.0	5.5
54	-0.3833	4.2875	0.09102	3.3	3.6	3.9	4.3	4.7	5.2	5.7
54.5	-0.3833	4.4179	0.09106	3.4	3.7	4.0	4.4	4.8	5.3	5.9
55	-0.3833	4.5498	0.09110	3.5	3.8	4.2	4.5	5.0	5.5	6.1
55.5	-0.3833	4.6827	0.09114	3.6	3.9	4.3	4.7	5.1	5.7	6.3
56	-0.3833	4.8162	0.09118	3.7	4.0	4.4	4.8	5.3	5.8	6.4
56.5	-0.3833	4.9500	0.09121	3.8	4.1	4.5	5.0	5.4	6.0	6.6
57	-0.3833	5.0837	0.09125	3.9	4.3	4.6	5.1	5.6	6.1	6.8
57.5	-0.3833	5.2173	0.09128	4.0	4.4	4.8	5.2	5.7	6.3	7.0
58	-0.3833	5.3507	0.09130	4.1	4.5	4.9	5.4	5.9	6.5	7.1
58.5	-0.3833	5.4834	0.09132	4.2	4.6	5.0	5.5	6.0	6.6	7.3
59	-0.3833	5.6151	0.09134	4.3	4.7	5.1	5.6	6.2	6.8	7.5
59.5	-0.3833	5.7454	0.09135	4.4	4.8	5.3	5.7	6.3	6.9	7.7
60	-0.3833	5.8742	0.09136	4.5	4.9	5.4	5.9	6.4	7.1	7.8
60.5	-0.3833	6.0014	0.09137	4.6	5.0	5.5	6.0	6.6	7.3	8.0
61	-0.3833	6.1270	0.09137	4.7	5.1	5.6	6.1	6.7	7.4	8.2
61.5	-0.3833	6.2511	0.09136	4.8	5.2	5.7	6.3	6.9	7.6	8.4
62	-0.3833	6.3738	0.09135	4.9	5.3	5.8	6.4	7.0	7.7	8.5
62.5	-0.3833	6.4948	0.09133	5.0	5.4	5.9	6.5	7.1	7.8	8.7
63	-0.3833	6.6144	0.09131	5.1	5.5	6.0	6.6	7.3	8.0	8.8
63.5	-0.3833	6.7328	0.09129	5.2	5.6	6.2	6.7	7.4	8.1	9.0
64	-0.3833	6.8501	0.09126	5.3	5.7	6.3	6.9	7.5	8.3	9.1
64.5	-0.3833	6.9662	0.09123	5.4	5.8	6.4	7.0	7.6	8.4	9.3
65	-0.3833	7.0812	0.09119	5.5	5.9	6.5	7.1	7.8	8.6	9.5
65.5	-0.3833	7.1950	0.09115	5.5	6.0	6.6	7.2	7.9	8.7	9.6
66	-0.3833	7.3076	0.09110	5.6	6.1	6.7	7.3	8.0	8.8	9.8
66.5	-0.3833	7.4189	0.09106	5.7	6.2	6.8	7.4	8.1	9.0	9.9
67	-0.3833	7.5288	0.09101	5.8	6.3	6.9	7.5	8.3	9.1	10.0
67.5	-0.3833	7.6375	0.09096	5.9	6.4	7.0	7.6	8.4	9.2	10.2
68	-0.3833	7.7448	0.09090	6.0	6.5	7.1	7.7	8.5	9.4	10.3
68.5	-0.3833	7.8509	0.09085	6.1	6.6	7.2	7.9	8.6	9.5	10.5
69	-0.3833	7.9559	0.09079	6.1	6.7	7.3	8.0	8.7	9.6	10.6
69.5	-0.3833	8.0599	0.09074	6.2	6.8	7.4	8.1	8.8	9.7	10.7
70	-0.3833	8.1630	0.09068	6.3	6.9	7.5	8.2	9.0	9.9	10.9
70.5	-0.3833	8.2651	0.09062	6.4	6.9	7.6	8.3	9.1	10.0	11.0
71	-0.3833	8.3666	0.09056	6.5	7.0	7.7	8.4	9.2	10.1	11.1
71.5	-0.3833	8.4676	0.09050	6.5	7.1	7.7	8.5	9.3	10.2	11.3
72	-0.3833	8.5679	0.09043	6.6	7.2	7.8	8.6	9.4	10.3	11.4
72.5	-0.3833	8.6674	0.09037	6.7	7.3	7.9	8.7	9.5	10.5	11.5
73	-0.3833	8.7661	0.09031	6.8	7.4	8.0	8.8	9.6	10.6	11.7
73.5	-0.3833	8.8638	0.09025	6.9	7.4	8.1	8.9	9.7	10.7	11.8
74	-0.3833	8.9601	0.09018	6.9	7.5	8.2	9.0	9.8	10.8	11.9
74.5	-0.3833	9.0552	0.09012	7.0	7.6	8.3	9.1	9.9	10.9	12.0
75	-0.3833	9.1490	0.09005	7.1	7.7	8.4	9.1	10.0	11.0	12.2
75.5	-0.3833	9.2418	0.08999	7.1	7.8	8.5	9.2	10.1	11.1	12.3
76	-0.3833	9.3337	0.08992	7.2	7.8	8.5	9.3	10.2	11.2	12.4
76.5	-0.3833	9.4252	0.08985	7.3	7.9	8.6	9.4	10.3	11.4	12.5
77	-0.3833	9.5166	0.08979	7.4	8.0	8.7	9.5	10.4	11.5	12.6
77.5	-0.3833	9.6086	0.08972	7.4	8.1	8.8	9.6	10.5	11.6	12.8
78	-0.3833	9.7015	0.08965	7.5	8.2	8.9	9.7	10.6	11.7	12.9
78.5	-0.3833	9.7957	0.08959	7.6	8.2	9.0	9.8	10.7	11.8	13.0

79	-0.3833	9.8915	0.08952	7.7	8.3	9.1	9.9	10.8	11.9	13.1
79.5	-0.3833	9.9892	0.08946	7.7	8.4	9.1	10.0	10.9	12.0	13.3
80	-0.3833	10.0891	0.08940	7.8	8.5	9.2	10.1	11.0	12.1	13.4
80.5	-0.3833	10.1916	0.08934	7.9	8.6	9.3	10.2	11.2	12.3	13.5
81	-0.3833	10.2965	0.08928	8.0	8.7	9.4	10.3	11.3	12.4	13.7
81.5	-0.3833	10.4041	0.08923	8.1	8.8	9.5	10.4	11.4	12.5	13.8
82	-0.3833	10.5140	0.08918	8.1	8.8	9.6	10.5	11.5	12.6	13.9
82.5	-0.3833	10.6263	0.08914	8.2	8.9	9.7	10.6	11.6	12.8	14.1
83	-0.3833	10.7410	0.08910	8.3	9.0	9.8	10.7	11.8	12.9	14.2
83.5	-0.3833	10.8578	0.08906	8.4	9.1	9.9	10.9	11.9	13.1	14.4
84	-0.3833	10.9767	0.08903	8.5	9.2	10.1	11.0	12.0	13.2	14.5
84.5	-0.3833	11.0974	0.08900	8.6	9.3	10.2	11.1	12.1	13.3	14.7
85	-0.3833	11.2198	0.08898	8.7	9.4	10.3	11.2	12.3	13.5	14.9
85.5	-0.3833	11.3435	0.08897	8.8	9.5	10.4	11.3	12.4	13.6	15.0
86	-0.3833	11.4684	0.08895	8.9	9.7	10.5	11.5	12.6	13.8	15.2
86.5	-0.3833	11.5940	0.08895	9.0	9.8	10.6	11.6	12.7	13.9	15.4
87	-0.3833	11.7201	0.08895	9.1	9.9	10.7	11.7	12.8	14.1	15.5
87.5	-0.3833	11.8461	0.08895	9.2	10.0	10.9	11.8	13.0	14.2	15.7
88	-0.3833	11.9720	0.08896	9.3	10.1	11.0	12.0	13.1	14.4	15.9
88.5	-0.3833	12.0976	0.08898	9.4	10.2	11.1	12.1	13.2	14.5	16.0
89	-0.3833	12.2229	0.08900	9.5	10.3	11.2	12.2	13.4	14.7	16.2
89.5	-0.3833	12.3477	0.08903	9.6	10.4	11.3	12.3	13.5	14.8	16.4
90	-0.3833	12.4723	0.08906	9.7	10.5	11.4	12.5	13.7	15.0	16.5
90.5	-0.3833	12.5965	0.08909	9.8	10.6	11.5	12.6	13.8	15.1	16.7
91	-0.3833	12.7205	0.08913	9.9	10.7	11.7	12.7	13.9	15.3	16.9
91.5	-0.3833	12.8443	0.08918	10.0	10.8	11.8	12.8	14.1	15.5	17.0
92	-0.3833	12.9681	0.08923	10.1	10.9	11.9	13.0	14.2	15.6	17.2
92.5	-0.3833	13.0920	0.08928	10.1	11.0	12.0	13.1	14.3	15.8	17.4
93	-0.3833	13.2158	0.08934	10.2	11.1	12.1	13.2	14.5	15.9	17.5
93.5	-0.3833	13.3399	0.08941	10.3	11.2	12.2	13.3	14.6	16.1	17.7
94	-0.3833	13.4643	0.08948	10.4	11.3	12.3	13.5	14.7	16.2	17.9
94.5	-0.3833	13.5892	0.08955	10.5	11.4	12.4	13.6	14.9	16.4	18.0
95	-0.3833	13.7146	0.08963	10.6	11.5	12.6	13.7	15.0	16.5	18.2
95.5	-0.3833	13.8408	0.08972	10.7	11.6	12.7	13.8	15.2	16.7	18.4
96	-0.3833	13.9676	0.08981	10.8	11.7	12.8	14.0	15.3	16.8	18.6
96.5	-0.3833	14.0953	0.08990	10.9	11.8	12.9	14.1	15.4	17.0	18.7
97	-0.3833	14.2239	0.09000	11.0	12.0	13.0	14.2	15.6	17.1	18.9
97.5	-0.3833	14.3537	0.09010	11.1	12.1	13.1	14.4	15.7	17.3	19.1
98	-0.3833	14.4848	0.09021	11.2	12.2	13.3	14.5	15.9	17.5	19.3
98.5	-0.3833	14.6174	0.09033	11.3	12.3	13.4	14.6	16.0	17.6	19.5
99	-0.3833	14.7519	0.09044	11.4	12.4	13.5	14.8	16.2	17.8	19.6
99.5	-0.3833	14.8882	0.09057	11.5	12.5	13.6	14.9	16.3	18.0	19.8
100	-0.3833	15.0267	0.09069	11.6	12.6	13.7	15.0	16.5	18.1	20.0
100.5	-0.3833	15.1676	0.09083	11.7	12.7	13.9	15.2	16.6	18.3	20.2
101	-0.3833	15.3108	0.09096	11.8	12.8	14.0	15.3	16.8	18.5	20.4
101.5	-0.3833	15.4564	0.09110	11.9	13.0	14.1	15.5	17.0	18.7	20.6
102	-0.3833	15.6046	0.09125	12.0	13.1	14.3	15.6	17.1	18.9	20.8
102.5	-0.3833	15.7553	0.09139	12.1	13.2	14.4	15.8	17.3	19.0	21.0
103	-0.3833	15.9087	0.09155	12.3	13.3	14.5	15.9	17.5	19.2	21.3
103.5	-0.3833	16.0645	0.09170	12.4	13.5	14.7	16.1	17.6	19.4	21.5
104	-0.3833	16.2229	0.09186	12.5	13.6	14.8	16.2	17.8	19.6	21.7
104.5	-0.3833	16.3837	0.09203	12.6	13.7	15.0	16.4	18.0	19.8	21.9
105	-0.3833	16.5470	0.09219	12.7	13.8	15.1	16.5	18.2	20.0	22.2
105.5	-0.3833	16.7129	0.09236	12.8	14.0	15.3	16.7	18.4	20.2	22.4
106	-0.3833	16.8814	0.09254	13.0	14.1	15.4	16.9	18.5	20.5	22.6
106.5	-0.3833	17.0527	0.09271	13.1	14.3	15.6	17.1	18.7	20.7	22.9
107	-0.3833	17.2269	0.09289	13.2	14.4	15.7	17.2	18.9	20.9	23.1
107.5	-0.3833	17.4039	0.09307	13.3	14.5	15.9	17.4	19.1	21.1	23.4
108	-0.3833	17.5839	0.09326	13.5	14.7	16.0	17.6	19.3	21.3	23.6
108.5	-0.3833	17.7668	0.09344	13.6	14.8	16.2	17.8	19.5	21.6	23.9
109	-0.3833	17.9526	0.09363	13.7	15.0	16.4	18.0	19.7	21.8	24.2
109.5	-0.3833	18.1412	0.09382	13.9	15.1	16.5	18.1	20.0	22.0	24.4
110	-0.3833	18.3324	0.09401	14.0	15.3	16.7	18.3	20.2	22.3	24.7

Length	L	M	S	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2	SD3
45	-0.3521	2.441	0.09182	1.9	2	2.2	2.4	2.7	3	3.3
45.5	-0.3521	2.5244	0.09153	1.9	2.1	2.3	2.5	2.8	3.1	3.4
46	-0.3521	2.6077	0.09124	2	2.2	2.4	2.6	2.9	3.1	3.5
46.5	-0.3521	2.6913	0.09094	2.1	2.3	2.5	2.7	3	3.2	3.6
47	-0.3521	2.7755	0.09065	2.1	2.3	2.5	2.8	3	3.3	3.7
47.5	-0.3521	2.8609	0.09036	2.2	2.4	2.6	2.9	3.1	3.4	3.8
48	-0.3521	2.948	0.09007	2.3	2.5	2.7	2.9	3.2	3.6	3.9
48.5	-0.3521	3.0377	0.08977	2.3	2.6	2.8	3	3.3	3.7	4
49	-0.3521	3.1308	0.08948	2.4	2.6	2.9	3.1	3.4	3.8	4.2
49.5	-0.3521	3.2276	0.08919	2.5	2.7	3	3.2	3.5	3.9	4.3
50	-0.3521	3.3278	0.0889	2.6	2.8	3	3.3	3.6	4	4.4
50.5	-0.3521	3.4311	0.08861	2.7	2.9	3.1	3.4	3.8	4.1	4.5
51	-0.3521	3.5376	0.08831	2.7	3	3.2	3.5	3.9	4.2	4.7
51.5	-0.3521	3.6477	0.08801	2.8	3.1	3.3	3.6	4	4.4	4.8
52	-0.3521	3.762	0.08771	2.9	3.2	3.5	3.8	4.1	4.5	5
52.5	-0.3521	3.8814	0.08741	3	3.3	3.6	3.9	4.2	4.6	5.1
53	-0.3521	4.006	0.08711	3.1	3.4	3.7	4	4.4	4.8	5.3
53.5	-0.3521	4.1354	0.08681	3.2	3.5	3.8	4.1	4.5	4.9	5.4
54	-0.3521	4.2693	0.08651	3.3	3.6	3.9	4.3	4.7	5.1	5.6
54.5	-0.3521	4.4066	0.08621	3.4	3.7	4	4.4	4.8	5.3	5.8
55	-0.3521	4.5467	0.08592	3.6	3.8	4.2	4.5	5	5.4	6
55.5	-0.3521	4.6892	0.08563	3.7	4	4.3	4.7	5.1	5.6	6.1
56	-0.3521	4.8338	0.08535	3.8	4.1	4.4	4.8	5.3	5.8	6.3
56.5	-0.3521	4.9796	0.08507	3.9	4.2	4.6	5	5.4	5.9	6.5
57	-0.3521	5.1259	0.08481	4	4.3	4.7	5.1	5.6	6.1	6.7
57.5	-0.3521	5.2721	0.08455	4.1	4.5	4.9	5.3	5.7	6.3	6.9
58	-0.3521	5.418	0.0843	4.3	4.6	5	5.4	5.9	6.4	7.1
58.5	-0.3521	5.5632	0.08406	4.4	4.7	5.1	5.6	6.1	6.6	7.2
59	-0.3521	5.7074	0.08383	4.5	4.8	5.3	5.7	6.2	6.8	7.4
59.5	-0.3521	5.8501	0.08362	4.6	5	5.4	5.9	6.4	7	7.6
60	-0.3521	5.9907	0.08342	4.7	5.1	5.5	6	6.5	7.1	7.8
60.5	-0.3521	6.1284	0.08324	4.8	5.2	5.6	6.1	6.7	7.3	8
61	-0.3521	6.2632	0.08308	4.9	5.3	5.8	6.3	6.8	7.4	8.1
61.5	-0.3521	6.3954	0.08292	5	5.4	5.9	6.4	7	7.6	8.3
62	-0.3521	6.5251	0.08279	5.1	5.6	6	6.5	7.1	7.7	8.5
62.5	-0.3521	6.6527	0.08266	5.2	5.7	6.1	6.7	7.2	7.9	8.6
63	-0.3521	6.7786	0.08255	5.3	5.8	6.2	6.8	7.4	8	8.8
63.5	-0.3521	6.9028	0.08245	5.4	5.9	6.4	6.9	7.5	8.2	8.9
64	-0.3521	7.0255	0.08236	5.5	6	6.5	7	7.6	8.3	9.1
64.5	-0.3521	7.1467	0.08229	5.6	6.1	6.6	7.1	7.8	8.5	9.3
65	-0.3521	7.2666	0.08223	5.7	6.2	6.7	7.3	7.9	8.6	9.4
65.5	-0.3521	7.3854	0.08218	5.8	6.3	6.8	7.4	8	8.7	9.6
66	-0.3521	7.5034	0.08215	5.9	6.4	6.9	7.5	8.2	8.9	9.7
66.5	-0.3521	7.6206	0.08213	6	6.5	7	7.6	8.3	9	9.9
67	-0.3521	7.737	0.08212	6.1	6.6	7.1	7.7	8.4	9.2	10
67.5	-0.3521	7.8526	0.08212	6.2	6.7	7.2	7.9	8.5	9.3	10.2
68	-0.3521	7.9674	0.08214	6.3	6.8	7.3	8	8.7	9.4	10.3
68.5	-0.3521	8.0816	0.08216	6.4	6.9	7.5	8.1	8.8	9.6	10.5
69	-0.3521	8.1955	0.08219	6.5	7	7.6	8.2	8.9	9.7	10.6
69.5	-0.3521	8.3092	0.08224	6.6	7.1	7.7	8.3	9	9.8	10.8
70	-0.3521	8.4227	0.08229	6.6	7.2	7.8	8.4	9.2	10	10.9
70.5	-0.3521	8.5358	0.08235	6.7	7.3	7.9	8.5	9.3	10.1	11.1
71	-0.3521	8.648	0.08241	6.8	7.4	8	8.6	9.4	10.2	11.2
71.5	-0.3521	8.7594	0.08248	6.9	7.5	8.1	8.8	9.5	10.4	11.3
72	-0.3521	8.8697	0.08254	7	7.6	8.2	8.9	9.6	10.5	11.5
72.5	-0.3521	8.9788	0.08262	7.1	7.6	8.3	9	9.8	10.6	11.6
73	-0.3521	9.0865	0.08269	7.2	7.7	8.4	9.1	9.9	10.8	11.8
73.5	-0.3521	9.1927	0.08276	7.2	7.8	8.5	9.2	10	10.9	11.9
74	-0.3521	9.2974	0.08283	7.3	7.9	8.6	9.3	10.1	11	12.1
74.5	-0.3521	9.401	0.08289	7.4	8	8.7	9.4	10.2	11.2	12.2
75	-0.3521	9.5032	0.08295	7.5	8.1	8.8	9.5	10.3	11.3	12.3
75.5	-0.3521	9.6041	0.08301	7.6	8.2	8.8	9.6	10.4	11.4	12.5
76	-0.3521	9.7033	0.08307	7.6	8.3	8.9	9.7	10.6	11.5	12.6
76.5	-0.3521	9.8007	0.08311	7.7	8.3	9	9.8	10.7	11.6	12.7
77	-0.3521	9.8963	0.08314	7.8	8.4	9.1	9.9	10.8	11.7	12.8
77.5	-0.3521	9.9902	0.08317	7.9	8.5	9.2	10	10.9	11.9	13
78	-0.3521	10.0827	0.08318	7.9	8.6	9.3	10.1	11	12	13.1
78.5	-0.3521	10.1741	0.08318	8	8.7	9.4	10.2	11.1	12.1	13.2

79	-0.3521	10.2649	0.08316	8.1	8.7	9.5	10.3	11.2	12.2	13.3
79.5	-0.3521	10.3558	0.08313	8.2	8.8	9.5	10.4	11.3	12.3	13.4
80	-0.3521	10.4475	0.08308	8.2	8.9	9.6	10.4	11.4	12.4	13.6
80.5	-0.3521	10.5405	0.08301	8.3	9	9.7	10.5	11.5	12.5	13.7
81	-0.3521	10.6352	0.08293	8.4	9.1	9.8	10.6	11.6	12.6	13.8
81.5	-0.3521	10.7322	0.08284	8.5	9.1	9.9	10.7	11.7	12.7	13.9
82	-0.3521	10.8321	0.08273	8.5	9.2	10	10.8	11.8	12.8	14
82.5	-0.3521	10.935	0.0826	8.6	9.3	10.1	10.9	11.9	13	14.2
83	-0.3521	11.0415	0.08246	8.7	9.4	10.2	11	12	13.1	14.3
83.5	-0.3521	11.1516	0.08231	8.8	9.5	10.3	11.2	12.1	13.2	14.4
84	-0.3521	11.2651	0.08215	8.9	9.6	10.4	11.3	12.2	13.3	14.6
84.5	-0.3521	11.3817	0.08198	9	9.7	10.5	11.4	12.4	13.5	14.7
85	-0.3521	11.5007	0.08181	9.1	9.8	10.6	11.5	12.5	13.6	14.9
85.5	-0.3521	11.6218	0.08163	9.2	9.9	10.7	11.6	12.6	13.7	15
86	-0.3521	11.7444	0.08145	9.3	10	10.8	11.7	12.8	13.9	15.2
86.5	-0.3521	11.8678	0.08128	9.4	10.1	11	11.9	12.9	14	15.3
87	-0.3521	11.9916	0.08111	9.5	10.2	11.1	12	13	14.2	15.5
87.5	-0.3521	12.1152	0.08096	9.6	10.4	11.2	12.1	13.2	14.3	15.6
88	-0.3521	12.2382	0.08082	9.7	10.5	11.3	12.2	13.3	14.5	15.8
88.5	-0.3521	12.3603	0.08069	9.8	10.6	11.4	12.4	13.4	14.6	15.9
89	-0.3521	12.4815	0.08058	9.9	10.7	11.5	12.5	13.5	14.7	16.1
89.5	-0.3521	12.6017	0.08048	10	10.8	11.6	12.6	13.7	14.9	16.2
90	-0.3521	12.7209	0.08041	10.1	10.9	11.8	12.7	13.8	15	16.4
90.5	-0.3521	12.8392	0.08034	10.2	11	11.9	12.8	13.9	15.1	16.5
91	-0.3521	12.9569	0.0803	10.3	11.1	12	13	14.1	15.3	16.7
91.5	-0.3521	13.0742	0.08026	10.4	11.2	12.1	13.1	14.2	15.4	16.8
92	-0.3521	13.191	0.08025	10.5	11.3	12.2	13.2	14.3	15.6	17
92.5	-0.3521	13.3075	0.08025	10.6	11.4	12.3	13.3	14.4	15.7	17.1
93	-0.3521	13.4239	0.08026	10.7	11.5	12.4	13.4	14.6	15.8	17.3
93.5	-0.3521	13.5404	0.08029	10.7	11.6	12.5	13.5	14.7	16	17.4
94	-0.3521	13.6572	0.08034	10.8	11.7	12.6	13.7	14.8	16.1	17.6
94.5	-0.3521	13.7746	0.0804	10.9	11.8	12.7	13.8	14.9	16.3	17.7
95	-0.3521	13.8928	0.08047	11	11.9	12.8	13.9	15.1	16.4	17.9
95.5	-0.3521	14.012	0.08056	11.1	12	12.9	14	15.2	16.5	18
96	-0.3521	14.1325	0.08067	11.2	12.1	13.1	14.1	15.3	16.7	18.2
96.5	-0.3521	14.2544	0.08078	11.3	12.2	13.2	14.3	15.5	16.8	18.4
97	-0.3521	14.3782	0.08092	11.4	12.3	13.3	14.4	15.6	17	18.5
97.5	-0.3521	14.5038	0.08106	11.5	12.4	13.4	14.5	15.7	17.1	18.7
98	-0.3521	14.6316	0.08122	11.6	12.5	13.5	14.6	15.9	17.3	18.9
98.5	-0.3521	14.7614	0.08139	11.7	12.6	13.6	14.8	16	17.5	19.1
99	-0.3521	14.8934	0.08157	11.8	12.7	13.7	14.9	16.2	17.6	19.2
99.5	-0.3521	15.0275	0.08177	11.9	12.8	13.9	15	16.3	17.8	19.4
100	-0.3521	15.1637	0.08198	12	12.9	14	15.2	16.5	18	19.6
100.5	-0.3521	15.3018	0.0822	12.1	13	14.1	15.3	16.6	18.1	19.8
101	-0.3521	15.4419	0.08243	12.2	13.2	14.2	15.4	16.8	18.3	20
101.5	-0.3521	15.5838	0.08267	12.3	13.3	14.4	15.6	16.9	18.5	20.2
102	-0.3521	15.7276	0.08292	12.4	13.4	14.5	15.7	17.1	18.7	20.4
102.5	-0.3521	15.8732	0.08317	12.5	13.5	14.6	15.9	17.3	18.8	20.6
103	-0.3521	16.0206	0.08343	12.6	13.6	14.8	16	17.4	19	20.8
103.5	-0.3521	16.1697	0.0837	12.7	13.7	14.9	16.2	17.6	19.2	21
104	-0.3521	16.3204	0.08397	12.8	13.9	15	16.3	17.8	19.4	21.2
104.5	-0.3521	16.4728	0.08425	12.9	14	15.2	16.5	17.9	19.6	21.5
105	-0.3521	16.6268	0.08453	13	14.1	15.3	16.6	18.1	19.8	21.7
105.5	-0.3521	16.7826	0.08481	13.2	14.2	15.4	16.8	18.3	20	21.9
106	-0.3521	16.9401	0.0851	13.3	14.4	15.6	16.9	18.5	20.2	22.1
106.5	-0.3521	17.0995	0.08539	13.4	14.5	15.7	17.1	18.6	20.4	22.4
107	-0.3521	17.2607	0.08568	13.5	14.6	15.9	17.3	18.8	20.6	22.6
107.5	-0.3521	17.4237	0.08599	13.6	14.7	16	17.4	19	20.8	22.8
108	-0.3521	17.5885	0.08629	13.7	14.9	16.2	17.6	19.2	21	23.1
108.5	-0.3521	17.7553	0.0866	13.8	15	16.3	17.8	19.4	21.2	23.3
109	-0.3521	17.9242	0.08691	14	15.1	16.5	17.9	19.6	21.4	23.6
109.5	-0.3521	18.0954	0.08723	14.1	15.3	16.6	18.1	19.8	21.7	23.8
110	-0.3521	18.2689	0.08755	14.2	15.4	16.8	18.3	20	21.9	24.1

Height	L	M	S	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2	SD3
65	-0.3833	7.2402	0.09113	5.6	6.1	6.6	7.2	7.9	8.7	9.7
65.5	-0.3833	7.3523	0.09109	5.7	6.2	6.7	7.4	8.1	8.9	9.8
66	-0.3833	7.4630	0.09104	5.8	6.3	6.8	7.5	8.2	9.0	10.0
66.5	-0.3833	7.5724	0.09099	5.8	6.4	6.9	7.6	8.3	9.1	10.1
67	-0.3833	7.6806	0.09094	5.9	6.4	7.0	7.7	8.4	9.3	10.2
67.5	-0.3833	7.7874	0.09088	6.0	6.5	7.1	7.8	8.5	9.4	10.4
68	-0.3833	7.8930	0.09083	6.1	6.6	7.2	7.9	8.7	9.5	10.5
68.5	-0.3833	7.9976	0.09077	6.2	6.7	7.3	8.0	8.8	9.7	10.7
69	-0.3833	8.1012	0.09071	6.3	6.8	7.4	8.1	8.9	9.8	10.8
69.5	-0.3833	8.2039	0.09065	6.3	6.9	7.5	8.2	9.0	9.9	10.9
70	-0.3833	8.3058	0.09059	6.4	7.0	7.6	8.3	9.1	10.0	11.1
70.5	-0.3833	8.4071	0.09053	6.5	7.1	7.7	8.4	9.2	10.1	11.2
71	-0.3833	8.5078	0.09047	6.6	7.1	7.8	8.5	9.3	10.3	11.3
71.5	-0.3833	8.6078	0.09041	6.7	7.2	7.9	8.6	9.4	10.4	11.5
72	-0.3833	8.7070	0.09035	6.7	7.3	8.0	8.7	9.5	10.5	11.6
72.5	-0.3833	8.8053	0.09028	6.8	7.4	8.1	8.8	9.7	10.6	11.7
73	-0.3833	8.9025	0.09022	6.9	7.5	8.1	8.9	9.8	10.7	11.8
73.5	-0.3833	8.9983	0.09016	7.0	7.6	8.2	9.0	9.9	10.8	12.0
74	-0.3833	9.0928	0.09009	7.0	7.6	8.3	9.1	10.0	11.0	12.1
74.5	-0.3833	9.1862	0.09003	7.1	7.7	8.4	9.2	10.1	11.1	12.2
75	-0.3833	9.2786	0.08996	7.2	7.8	8.5	9.3	10.2	11.2	12.3
75.5	-0.3833	9.3703	0.08989	7.2	7.9	8.6	9.4	10.3	11.3	12.5
76	-0.3833	9.4617	0.08983	7.3	8.0	8.7	9.5	10.4	11.4	12.6
76.5	-0.3833	9.5533	0.08976	7.4	8.0	8.7	9.6	10.5	11.5	12.7
77	-0.3833	9.6456	0.08969	7.5	8.1	8.8	9.6	10.6	11.6	12.8
77.5	-0.3833	9.7390	0.08963	7.5	8.2	8.9	9.7	10.7	11.7	12.9
78	-0.3833	9.8338	0.08956	7.6	8.3	9.0	9.8	10.8	11.8	13.1
78.5	-0.3833	9.9303	0.08950	7.7	8.4	9.1	9.9	10.9	12.0	13.2
79	-0.3833	10.0289	0.08943	7.8	8.4	9.2	10.0	11.0	12.1	13.3
79.5	-0.3833	10.1298	0.08937	7.8	8.5	9.3	10.1	11.1	12.2	13.4
80	-0.3833	10.2332	0.08932	7.9	8.6	9.4	10.2	11.2	12.3	13.6
80.5	-0.3833	10.3393	0.08926	8.0	8.7	9.5	10.3	11.3	12.4	13.7
81	-0.3833	10.4477	0.08921	8.1	8.8	9.6	10.4	11.4	12.6	13.9
81.5	-0.3833	10.5586	0.08916	8.2	8.9	9.7	10.6	11.6	12.7	14.0
82	-0.3833	10.6719	0.08912	8.3	9.0	9.8	10.7	11.7	12.8	14.1
82.5	-0.3833	10.7874	0.08908	8.4	9.1	9.9	10.8	11.8	13.0	14.3
83	-0.3833	10.9051	0.08905	8.5	9.2	10.0	10.9	11.9	13.1	14.5
83.5	-0.3833	11.0248	0.08902	8.5	9.3	10.1	11.0	12.1	13.3	14.6
84	-0.3833	11.1462	0.08899	8.6	9.4	10.2	11.1	12.2	13.4	14.8
84.5	-0.3833	11.2691	0.08897	8.7	9.5	10.3	11.3	12.3	13.5	14.9
85	-0.3833	11.3934	0.08896	8.8	9.6	10.4	11.4	12.5	13.7	15.1
85.5	-0.3833	11.5186	0.08895	8.9	9.7	10.6	11.5	12.6	13.8	15.3
86	-0.3833	11.6444	0.08895	9.0	9.8	10.7	11.6	12.7	14.0	15.4
86.5	-0.3833	11.7705	0.08895	9.1	9.9	10.8	11.8	12.9	14.2	15.6
87	-0.3833	11.8965	0.08896	9.2	10.0	10.9	11.9	13.0	14.3	15.8
87.5	-0.3833	12.0223	0.08897	9.3	10.1	11.0	12.0	13.2	14.5	15.9
88	-0.3833	12.1478	0.08899	9.4	10.2	11.1	12.1	13.3	14.6	16.1
88.5	-0.3833	12.2729	0.08901	9.5	10.3	11.2	12.3	13.4	14.8	16.3
89	-0.3833	12.3976	0.08904	9.6	10.4	11.4	12.4	13.6	14.9	16.4
89.5	-0.3833	12.5220	0.08907	9.7	10.5	11.5	12.5	13.7	15.1	16.6
90	-0.3833	12.6461	0.08911	9.8	10.6	11.6	12.6	13.8	15.2	16.8
90.5	-0.3833	12.7700	0.08915	9.9	10.7	11.7	12.8	14.0	15.4	16.9
91	-0.3833	12.8939	0.08920	10.0	10.9	11.8	12.9	14.1	15.5	17.1
91.5	-0.3833	13.0177	0.08925	10.1	11.0	11.9	13.0	14.3	15.7	17.3
92	-0.3833	13.1415	0.08931	10.2	11.1	12.0	13.1	14.4	15.8	17.4
92.5	-0.3833	13.2654	0.08937	10.3	11.2	12.1	13.3	14.5	16.0	17.6
93	-0.3833	13.3896	0.08944	10.4	11.3	12.3	13.4	14.7	16.1	17.8
93.5	-0.3833	13.5142	0.08951	10.5	11.4	12.4	13.5	14.8	16.3	17.9
94	-0.3833	13.6393	0.08959	10.6	11.5	12.5	13.6	14.9	16.4	18.1
94.5	-0.3833	13.7650	0.08967	10.7	11.6	12.6	13.8	15.1	16.6	18.3
95	-0.3833	13.8914	0.08975	10.8	11.7	12.7	13.9	15.2	16.7	18.5
95.5	-0.3833	14.0186	0.08984	10.8	11.8	12.8	14.0	15.4	16.9	18.6
96	-0.3833	14.1466	0.08994	10.9	11.9	12.9	14.1	15.5	17.0	18.8
96.5	-0.3833	14.2757	0.09004	11.0	12.0	13.1	14.3	15.6	17.2	19.0
97	-0.3833	14.4059	0.09015	11.1	12.1	13.2	14.4	15.8	17.4	19.2
97.5	-0.3833	14.5376	0.09026	11.2	12.2	13.3	14.5	15.9	17.5	19.3
98	-0.3833	14.6710	0.09037	11.3	12.3	13.4	14.7	16.1	17.7	19.5
98.5	-0.3833	14.8062	0.09049	11.4	12.4	13.5	14.8	16.2	17.9	19.7

99	-0.3833	14.9434	0.09062	11.5	12.5	13.7	14.9	16.4	18.0	19.9
99.5	-0.3833	15.0828	0.09075	11.6	12.7	13.8	15.1	16.5	18.2	20.1
100	-0.3833	15.2246	0.09088	11.7	12.8	13.9	15.2	16.7	18.4	20.3
100.5	-0.3833	15.3687	0.09102	11.9	12.9	14.1	15.4	16.9	18.6	20.5
101	-0.3833	15.5154	0.09116	12.0	13.0	14.2	15.5	17.0	18.7	20.7
101.5	-0.3833	15.6646	0.09131	12.1	13.1	14.3	15.7	17.2	18.9	20.9
102	-0.3833	15.8164	0.09146	12.2	13.3	14.5	15.8	17.4	19.1	21.1
102.5	-0.3833	15.9707	0.09161	12.3	13.4	14.6	16.0	17.5	19.3	21.4
103	-0.3833	16.1276	0.09177	12.4	13.5	14.7	16.1	17.7	19.5	21.6
103.5	-0.3833	16.2870	0.09193	12.5	13.6	14.9	16.3	17.9	19.7	21.8
104	-0.3833	16.4488	0.09209	12.6	13.8	15.0	16.4	18.1	19.9	22.0
104.5	-0.3833	16.6131	0.09226	12.8	13.9	15.2	16.6	18.2	20.1	22.3
105	-0.3833	16.7800	0.09243	12.9	14.0	15.3	16.8	18.4	20.3	22.5
105.5	-0.3833	16.9496	0.09261	13.0	14.2	15.5	16.9	18.6	20.5	22.7
106	-0.3833	17.1220	0.09278	13.1	14.3	15.6	17.1	18.8	20.8	23.0
106.5	-0.3833	17.2973	0.09296	13.3	14.5	15.8	17.3	19.0	21.0	23.2
107	-0.3833	17.4755	0.09315	13.4	14.6	15.9	17.5	19.2	21.2	23.5
107.5	-0.3833	17.6567	0.09333	13.5	14.7	16.1	17.7	19.4	21.4	23.7
108	-0.3833	17.8407	0.09352	13.7	14.9	16.3	17.8	19.6	21.7	24.0
108.5	-0.3833	18.0277	0.09371	13.8	15.0	16.4	18.0	19.8	21.9	24.3
109	-0.3833	18.2174	0.09390	13.9	15.2	16.6	18.2	20.0	22.1	24.5
109.5	-0.3833	18.4096	0.09409	14.1	15.4	16.8	18.4	20.3	22.4	24.8
110	-0.3833	18.6043	0.09428	14.2	15.5	17.0	18.6	20.5	22.6	25.1
110.5	-0.3833	18.8015	0.09448	14.4	15.7	17.1	18.8	20.7	22.9	25.4
111	-0.3833	19.0009	0.09467	14.5	15.8	17.3	19.0	20.9	23.1	25.7
111.5	-0.3833	19.2024	0.09487	14.7	16.0	17.5	19.2	21.2	23.4	26.0
112	-0.3833	19.4060	0.09507	14.8	16.2	17.7	19.4	21.4	23.6	26.2
112.5	-0.3833	19.6116	0.09527	15.0	16.3	17.9	19.6	21.6	23.9	26.5
113	-0.3833	19.8190	0.09546	15.1	16.5	18.0	19.8	21.8	24.2	26.8
113.5	-0.3833	20.0280	0.09566	15.3	16.7	18.2	20.0	22.1	24.4	27.1
114	-0.3833	20.2385	0.09586	15.4	16.8	18.4	20.2	22.3	24.7	27.4
114.5	-0.3833	20.4502	0.09606	15.6	17.0	18.6	20.5	22.6	25.0	27.8
115	-0.3833	20.6629	0.09626	15.7	17.2	18.8	20.7	22.8	25.2	28.1
115.5	-0.3833	20.8766	0.09646	15.9	17.3	19.0	20.9	23.0	25.5	28.4
116	-0.3833	21.0909	0.09666	16.0	17.5	19.2	21.1	23.3	25.8	28.7
116.5	-0.3833	21.3059	0.09686	16.2	17.7	19.4	21.3	23.5	26.1	29.0
117	-0.3833	21.5213	0.09707	16.3	17.8	19.6	21.5	23.8	26.3	29.3
117.5	-0.3833	21.7370	0.09727	16.5	18.0	19.8	21.7	24.0	26.6	29.6
118	-0.3833	21.9529	0.09747	16.6	18.2	19.9	22.0	24.2	26.9	29.9
118.5	-0.3833	22.1690	0.09767	16.8	18.4	20.1	22.2	24.5	27.2	30.3
119	-0.3833	22.3851	0.09788	16.9	18.5	20.3	22.4	24.7	27.4	30.6
119.5	-0.3833	22.6012	0.09808	17.1	18.7	20.5	22.6	25.0	27.7	30.9
120	-0.3833	22.8173	0.09828	17.3	18.9	20.7	22.8	25.2	28.0	31.2

Height	L	M	S	SD3neg	SD2neg	SD1neg	SD0	SD1	SD2	SD3
65	-0.3521	7.4327	0.08217	5.9	6.3	6.9	7.4	8.1	8.8	9.6
65.5	-0.3521	7.5504	0.08214	6.0	6.4	7.0	7.6	8.2	8.9	9.8
66	-0.3521	7.6673	0.08212	6.1	6.5	7.1	7.7	8.3	9.1	9.9
66.5	-0.3521	7.7834	0.08212	6.1	6.6	7.2	7.8	8.5	9.2	10.1
67	-0.3521	7.8986	0.08213	6.2	6.7	7.3	7.9	8.6	9.4	10.2
67.5	-0.3521	8.0132	0.08214	6.3	6.8	7.4	8.0	8.7	9.5	10.4
68	-0.3521	8.1272	0.08217	6.4	6.9	7.5	8.1	8.8	9.6	10.5
68.5	-0.3521	8.2410	0.08221	6.5	7.0	7.6	8.2	9.0	9.8	10.7
69	-0.3521	8.3547	0.08226	6.6	7.1	7.7	8.4	9.1	9.9	10.8
69.5	-0.3521	8.4680	0.08231	6.7	7.2	7.8	8.5	9.2	10.0	11.0
70	-0.3521	8.5808	0.08237	6.8	7.3	7.9	8.6	9.3	10.2	11.1
70.5	-0.3521	8.6927	0.08243	6.9	7.4	8.0	8.7	9.5	10.3	11.3
71	-0.3521	8.8036	0.08250	6.9	7.5	8.1	8.8	9.6	10.4	11.4
71.5	-0.3521	8.9135	0.08257	7.0	7.6	8.2	8.9	9.7	10.6	11.6
72	-0.3521	9.0221	0.08264	7.1	7.7	8.3	9.0	9.8	10.7	11.7
72.5	-0.3521	9.1292	0.08272	7.2	7.8	8.4	9.1	9.9	10.8	11.8
73	-0.3521	9.2347	0.08278	7.3	7.9	8.5	9.2	10.0	11.0	12.0
73.5	-0.3521	9.3390	0.08285	7.4	7.9	8.6	9.3	10.2	11.1	12.1
74	-0.3521	9.4420	0.08292	7.4	8.0	8.7	9.4	10.3	11.2	12.2
74.5	-0.3521	9.5438	0.08298	7.5	8.1	8.8	9.5	10.4	11.3	12.4
75	-0.3521	9.6440	0.08303	7.6	8.2	8.9	9.6	10.5	11.4	12.5
75.5	-0.3521	9.7425	0.08308	7.7	8.3	9.0	9.7	10.6	11.6	12.6
76	-0.3521	9.8392	0.08312	7.7	8.4	9.1	9.8	10.7	11.7	12.8
76.5	-0.3521	9.9341	0.08315	7.8	8.5	9.2	9.9	10.8	11.8	12.9
77	-0.3521	10.0274	0.08317	7.9	8.5	9.2	10.0	10.9	11.9	13.0
77.5	-0.3521	10.1194	0.08318	8.0	8.6	9.3	10.1	11.0	12.0	13.1
78	-0.3521	10.2105	0.08317	8.0	8.7	9.4	10.2	11.1	12.1	13.3
78.5	-0.3521	10.3012	0.08315	8.1	8.8	9.5	10.3	11.2	12.2	13.4
79	-0.3521	10.3923	0.08311	8.2	8.8	9.6	10.4	11.3	12.3	13.5
79.5	-0.3521	10.4845	0.08305	8.3	8.9	9.7	10.5	11.4	12.4	13.6
80	-0.3521	10.5781	0.08298	8.3	9.0	9.7	10.6	11.5	12.6	13.7
80.5	-0.3521	10.6737	0.08290	8.4	9.1	9.8	10.7	11.6	12.7	13.8
81	-0.3521	10.7718	0.08279	8.5	9.2	9.9	10.8	11.7	12.8	14.0
81.5	-0.3521	10.8728	0.08268	8.6	9.3	10.0	10.9	11.8	12.9	14.1
82	-0.3521	10.9772	0.08255	8.7	9.3	10.1	11.0	11.9	13.0	14.2
82.5	-0.3521	11.0851	0.08241	8.7	9.4	10.2	11.1	12.1	13.1	14.4
83	-0.3521	11.1966	0.08225	8.8	9.5	10.3	11.2	12.2	13.3	14.5
83.5	-0.3521	11.3114	0.08209	8.9	9.6	10.4	11.3	12.3	13.4	14.6
84	-0.3521	11.4290	0.08191	9.0	9.7	10.5	11.4	12.4	13.5	14.8
84.5	-0.3521	11.5490	0.08174	9.1	9.9	10.7	11.5	12.5	13.7	14.9
85	-0.3521	11.6707	0.08156	9.2	10.0	10.8	11.7	12.7	13.8	15.1
85.5	-0.3521	11.7937	0.08138	9.3	10.1	10.9	11.8	12.8	13.9	15.2
86	-0.3521	11.9173	0.08121	9.4	10.2	11.0	11.9	12.9	14.1	15.4
86.5	-0.3521	12.0411	0.08105	9.5	10.3	11.1	12.0	13.1	14.2	15.5
87	-0.3521	12.1645	0.08090	9.6	10.4	11.2	12.2	13.2	14.4	15.7
87.5	-0.3521	12.2871	0.08076	9.7	10.5	11.3	12.3	13.3	14.5	15.8
88	-0.3521	12.4089	0.08064	9.8	10.6	11.5	12.4	13.5	14.7	16.0
88.5	-0.3521	12.5298	0.08054	9.9	10.7	11.6	12.5	13.6	14.8	16.1
89	-0.3521	12.6495	0.08045	10.0	10.8	11.7	12.6	13.7	14.9	16.3
89.5	-0.3521	12.7683	0.08038	10.1	10.9	11.8	12.8	13.9	15.1	16.4
90	-0.3521	12.8864	0.08032	10.2	11.0	11.9	12.9	14.0	15.2	16.6
90.5	-0.3521	13.0038	0.08028	10.3	11.1	12.0	13.0	14.1	15.3	16.7
91	-0.3521	13.1209	0.08025	10.4	11.2	12.1	13.1	14.2	15.5	16.9
91.5	-0.3521	13.2376	0.08024	10.5	11.3	12.2	13.2	14.4	15.6	17.0
92	-0.3521	13.3541	0.08025	10.6	11.4	12.3	13.4	14.5	15.8	17.2
92.5	-0.3521	13.4705	0.08027	10.7	11.5	12.4	13.5	14.6	15.9	17.3
93	-0.3521	13.5870	0.08031	10.8	11.6	12.6	13.6	14.7	16.0	17.5
93.5	-0.3521	13.7041	0.08036	10.9	11.7	12.7	13.7	14.9	16.2	17.6
94	-0.3521	13.8217	0.08043	11.0	11.8	12.8	13.8	15.0	16.3	17.8
94.5	-0.3521	13.9403	0.08051	11.1	11.9	12.9	13.9	15.1	16.5	17.9
95	-0.3521	14.0600	0.08060	11.1	12.0	13.0	14.1	15.3	16.6	18.1
95.5	-0.3521	14.1811	0.08071	11.2	12.1	13.1	14.2	15.4	16.7	18.3
96	-0.3521	14.3037	0.08083	11.3	12.2	13.2	14.3	15.5	16.9	18.4
96.5	-0.3521	14.4282	0.08097	11.4	12.3	13.3	14.4	15.7	17.0	18.6
97	-0.3521	14.5547	0.08112	11.5	12.4	13.4	14.6	15.8	17.2	18.8
97.5	-0.3521	14.6832	0.08129	11.6	12.5	13.6	14.7	15.9	17.4	18.9
98	-0.3521	14.8140	0.08146	11.7	12.6	13.7	14.8	16.1	17.5	19.1
98.5	-0.3521	14.9468	0.08165	11.8	12.8	13.8	14.9	16.2	17.7	19.3

99	-0.3521	15.0818	0.08185	11.9	12.9	13.9	15.1	16.4	17.9	19.5
99.5	-0.3521	15.2187	0.08206	12.0	13.0	14.0	15.2	16.5	18.0	19.7
100	-0.3521	15.3576	0.08229	12.1	13.1	14.2	15.4	16.7	18.2	19.9
100.5	-0.3521	15.4985	0.08252	12.2	13.2	14.3	15.5	16.9	18.4	20.1
101	-0.3521	15.6412	0.08277	12.3	13.3	14.4	15.6	17.0	18.5	20.3
101.5	-0.3521	15.7857	0.08302	12.4	13.4	14.5	15.8	17.2	18.7	20.5
102	-0.3521	15.9320	0.08328	12.5	13.6	14.7	15.9	17.3	18.9	20.7
102.5	-0.3521	16.0801	0.08354	12.6	13.7	14.8	16.1	17.5	19.1	20.9
103	-0.3521	16.2298	0.08381	12.8	13.8	14.9	16.2	17.7	19.3	21.1
103.5	-0.3521	16.3812	0.08408	12.9	13.9	15.1	16.4	17.8	19.5	21.3
104	-0.3521	16.5342	0.08436	13.0	14.0	15.2	16.5	18.0	19.7	21.6
104.5	-0.3521	16.6889	0.08464	13.1	14.2	15.4	16.7	18.2	19.9	21.8
105	-0.3521	16.8454	0.08493	13.2	14.3	15.5	16.8	18.4	20.1	22.0
105.5	-0.3521	17.0036	0.08521	13.3	14.4	15.6	17.0	18.5	20.3	22.2
106	-0.3521	17.1637	0.08551	13.4	14.5	15.8	17.2	18.7	20.5	22.5
106.5	-0.3521	17.3256	0.08580	13.5	14.7	15.9	17.3	18.9	20.7	22.7
107	-0.3521	17.4894	0.08611	13.7	14.8	16.1	17.5	19.1	20.9	22.9
107.5	-0.3521	17.6550	0.08641	13.8	14.9	16.2	17.7	19.3	21.1	23.2
108	-0.3521	17.8226	0.08673	13.9	15.1	16.4	17.8	19.5	21.3	23.4
108.5	-0.3521	17.9924	0.08704	14.0	15.2	16.5	18.0	19.7	21.5	23.7
109	-0.3521	18.1645	0.08736	14.1	15.3	16.7	18.2	19.8	21.8	23.9
109.5	-0.3521	18.3390	0.08768	14.3	15.5	16.8	18.3	20.0	22.0	24.2
110	-0.3521	18.5158	0.08800	14.4	15.6	17.0	18.5	20.2	22.2	24.4
110.5	-0.3521	18.6948	0.08832	14.5	15.8	17.1	18.7	20.4	22.4	24.7
111	-0.3521	18.8759	0.08864	14.6	15.9	17.3	18.9	20.7	22.7	25.0
111.5	-0.3521	19.0590	0.08896	14.8	16.0	17.5	19.1	20.9	22.9	25.2
112	-0.3521	19.2439	0.08928	14.9	16.2	17.6	19.2	21.1	23.1	25.5
112.5	-0.3521	19.4304	0.08960	15.0	16.3	17.8	19.4	21.3	23.4	25.8
113	-0.3521	19.6185	0.08991	15.2	16.5	18.0	19.6	21.5	23.6	26.0
113.5	-0.3521	19.8081	0.09022	15.3	16.6	18.1	19.8	21.7	23.9	26.3
114	-0.3521	19.9990	0.09054	15.4	16.8	18.3	20.0	21.9	24.1	26.6
114.5	-0.3521	20.1912	0.09085	15.6	16.9	18.5	20.2	22.1	24.4	26.9
115	-0.3521	20.3846	0.09116	15.7	17.1	18.6	20.4	22.4	24.6	27.2
115.5	-0.3521	20.5789	0.09147	15.8	17.2	18.8	20.6	22.6	24.9	27.5
116	-0.3521	20.7741	0.09177	16.0	17.4	19.0	20.8	22.8	25.1	27.8
116.5	-0.3521	20.9700	0.09208	16.1	17.5	19.2	21.0	23.0	25.4	28.0
117	-0.3521	21.1666	0.09239	16.2	17.7	19.3	21.2	23.3	25.6	28.3
117.5	-0.3521	21.3636	0.09270	16.4	17.9	19.5	21.4	23.5	25.9	28.6
118	-0.3521	21.5611	0.09300	16.5	18.0	19.7	21.6	23.7	26.1	28.9
118.5	-0.3521	21.7588	0.09331	16.7	18.2	19.9	21.8	23.9	26.4	29.2
119	-0.3521	21.9568	0.09362	16.8	18.3	20.0	22.0	24.1	26.6	29.5
119.5	-0.3521	22.1549	0.09393	16.9	18.5	20.2	22.2	24.4	26.9	29.8
120	-0.3521	22.3530	0.09424	17.1	18.6	20.4	22.4	24.6	27.2	30.1

Appendix G: Summary of biochemistry reference values

Test	Age (Male and Female Unless Specified)	Normal Range	Diagnosis	Diagnostic Values
Phosphorous (RCPCH, 2016:3)	< 1 year	1.3 – 2.6 mmol/L	Hypophosphataemia	< 1.3 mmol/L
	1 – 16 year	0.9 – 1.8 mmol/L		< 0.9 mmol/L
			RFS	Drop of > 0.16mmol/L to < 0.65mmol/L
Potassium (Parli et al., 2014:199; RCPCH, 2016:3)	Paediatric	3.5 – 5.5 mmol/L	Moderate hypokalaemia	< 3.5 mmol/L
			Severe Hypokalaemia	< 2.5 mmol/L
Magnesium (Meyer & Marino, 2015:78; RCPCH, 2016:3; Tresley & Sheean, 2008:2105)	Paediatric	0.6 – 1.0 mmol/L	Hypomagnesaemia	< 0.6 mmol/L
			Moderate to severe hypomagnesaemia	< 0.5 mmol/L
Calcium (RCPCH, 2016:3)	< 4 weeks	2.0 – 2.7 mmol/L	Hypocalcaemia	< 2.0 mmol/L
	4 weeks – 16 years	2.2 – 2.7 mmol/L		< 2.2 mmol/L
Sodium (RCPCH, 2016:3)	Paediatric	133 – 146 mmol/L	Hyponatraemia	< 133 mmol/L
Albumin (RCPCH, 2016:4)	< 4 weeks	25 – 45 g/L	Hypalbuminaemia	< 25 g/L
	4 weeks – 1 year	30 – 45 g/L		< 30 g/L
	1 – 16 years	35 – 50 g/L		< 35 g/L
CRP (RCPCH, 2016:7; Rytter et al., 2017:497)	Paediatric	< 5 mg/L	Risk for death	> 15 mg/L
Urea (RCPCH, 2016:3)	0 – 12 months	0.8 – 5.5 mmol/L	Elevated urea	> 5.5 mmol/L
	1 – 16 years	2.5 – 6.5 mmol/L		> 6.5 mmol/L
Creatinine (RCPCH, 2016:3)	Neonate[1]	21– 75 µmol/L	Elevated creatinine	> 75 µmol/L
	1 month – 4 years	13 – 39 µmol/L		> 39 µmol/L
Bilirubin (RCPCH, 2016:5)	14 days – 16 years	< 21 µmol/L	Deranged liver enzymes	> Normal range
ALP (RCPCH, 2016:5)	Neonate[1]	73- 391 IU/L		
	Infant	59 – 425 IU/L		
	1 – 14 years	76 – 308 IU/L		
GGT (RCPCH, 2016:5)	Paediatric	9 – 40 IU/L		
ALT (RCPCH, 2016:4)	0 – 12 months	0 – 41 IU/L		
	1 – 2 years	0 – 28 IU/L		
	3 – 6 years	0 – 29 IU/L		
AST (RCPCH, 2016:5)	Neonate[1]	18 – 92 IU/L		
	Child	8-60 IU/L		
Haemoglobin (WHO, 2011:3)	6 – 59 months	≥ 11g/dl	Anaemia	< 11 g/dl
			Severe anaemia	< 7 g/dl
Platelet count (Assinger & Shen, 2014:2; RCPCH, 2016:1)	Paediatric	150 – 450 ($\times 10^3$/µl)	Thrombocytopaenia	< 150 ($\times 10^3$/µl)
INR (RCPCH, 2016:2; De Maayer & Saloojee, 2011:3)	Paediatric	1	Poor prognostic factor for death	> 1.7

Appendix H: Author guidelines for SAJCH publication

SAJCH The South African Journal of Child Health

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Author Guidelines

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

To submit a manuscript, please proceed to the *SAJCH* Editorial Manager

should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

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Open access policy

SAJCH is DoHET accredited and accepted articles attract the DoHET subsidy.

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Impact

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met for an individual to be included as an author (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions. Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the

South Africa 2018 Report Card

» Paediatric nurse training activity in South Africa: A short report

» Trends in diarrhoeal disease hospitalisation in a paediatric short - stay ward at a tertiary-level hospital in Soweto: 2002-2016

» Epidemiological trend of post-neonatal tetanus in a Nigerian teaching hospital

» Workplace support for breastfeeding employees in educational and healthcare settings in Ghana

KEYWORDS

Breastfeeding
Child development

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this requirement are Editorials, Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

Review articles

Review articlesshould always be discussed with the Editor prior to submission.

Guideline word limit: 4 000 words

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author.
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) consecutively as they are referred to in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting..*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
  - On the Crossref homepage, paste the article title into the 'Metadata search' box.
  - Look for the correct, matching article in the list of results.
  - Click Actions > Cite
  - Alongside 'url =' copy the URL between { }.
  - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355.

http://dx/doi.org/10.1000/hgjr.182

- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

Appendix I: Author guidelines for SAJCN publication

SAJCN
THE SOUTH AFRICAN JOURNAL OF CLINICAL NUTRITION

Author instructions

All manuscripts and correspondence to be submitted electronically to: www.sajcn.co.za

Copyright

Material submitted for publication in the South African Journal of Clinical Nutrition (SAJCN) is accepted provided it has not been published elsewhere. Copyright forms will be sent with acknowledgement of receipt and the SAJCN reserves copyright of the material published. The SAJCN does not hold itself responsible for statements made by the authors.

Authorship

All named authors must give consent to publication. Authorship should be based only on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting the article or revising it critically for important intellectual content; (iii) final approval of the version to be published. All three of these conditions must be met (Uniform requirements for manuscripts submitted to biomedical journals; www.icmje.org/index.html).

Manuscripts

Short items are more likely to appeal to our readers and therefore to be accepted for publication. ***Manuscript should not exceed 4000 words in total all contents inclusive.***

Original articles of 4 000 words or less, with up to 6 tables or illustrations, should normally report observations or research of relevance to the field of nutrition. References should preferably be limited to no more than 25.

Short reports or scientific letters, which include case reports, side effects of nutrient supplements/drugs and brief or negative research findings should be 1000 words or less, with 1 table or illustration and no more than 6 references.

Editorials, Opinions, Issues in the field of nutrition. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJCN peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, if intended for the correspondence column, should be marked 'for publication', signed by all authors and presented in triple spacing. Letters should be no longer than 400 words with only one illustration or table.

Obituaries should not exceed 400 words and may be accompanied by a photograph.

Manuscript preparation

- Please submit your manuscript electronically at www.sajcn.co.za. (Register as an author, log in and follow the 5 steps to upload your manuscript.)
- Please submit the manuscript as a MS Windows Word document.
- Please have your manuscript edited by a language expert or colleague proficient in English prior to submission. Articles must be in UK English.
- All manuscripts must include an abstract (50-250 words).
- Research articles should have a structured abstract not exceeding 250 words (50 for short reports) comprising: Objectives, Design, Setting, Subjects, Outcome measures, Results and Conclusions.
- Refer to articles in recent issues for guidance on the presentation of headings and subheadings.
- Abbreviations should be spelt out when first used in the text and thereafter used consistently.
- Scientific measurements should be expressed in SI units except: blood pressure should be given in mmHg and haemoglobin values in g/dl.

If in doubt, refer to www.icmje.org/index.html

Illustrations

1. All illustrations must be submitted electronically. High resolution (300dpi) .jpg or .tiff files are preferred.
2. Figures consist of all material that cannot be set in type, such as photographs and line drawings.
3. Tables and legends for illustrations should appear on separate sheets and should be clearly identified.
4. Line drawings should be arranged to conserve vertical space. Note that reduction to 80 mm for a single column or 170 mm for double columns should not render lettering illegible. Explanations should be included in the legend and not on the figure itself.
5. Figure numbers should be clearly marked on the back of prints and the top of illustrations should be indicated.
6. If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder and the author(s).
7. A limited number of illustrations are free at the discretion of the editor. Colour illustrations are encouraged but are charged to the author.

References

References should be inserted in the text as superior numbers and should be listed at the end of the article in numerical and not in alphabetical order.

Authors are responsible for verification of references from the original sources.

References should be set out in the Vancouver style and approved abbreviations of journal titles used; consult the List of Journals in Index Medicus for these details.

Names and initials of all authors should be given unless there are more than six, in which case the first three names should be given followed by et al. First and last page numbers should be given.

Journal references should appear thus:

1. Price NC. Importance of asking about glaucoma. BMJ 1983; 286: 349-350. Book references should be set out as follows:

1. Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975: 96-101.
2. Wainstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974: 457-472.

Manuscripts accepted but not yet published can be included as references followed by (in press).

Unpublished observations and personal communications may be cited in the text, but not in the reference list.

Manuscript revisions

In the event of a manuscript needing revision following the peer review process, all revision changes to the original manuscript should be made using the "track changes" function in Microsoft Word, or in any other such similar format so as to facilitate the speedy completion of the review process. In the event of an "author-reviewer" difference of opinion, the author(s) should state their opinion in writing in the text, which should be bracketed. Revised manuscripts which do not conform to this revision format will be returned to the authors for editing.

Revised manuscript should be resubmitted electronically within 3 weeks of receipt thereof.

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Galley proofs will be forwarded to the author before publication and if not returned, it will be regarded as approved. Please note that alterations to typeset articles are costly and will be charged to the authors.

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