THE IMPACT OF HIV ON SEVERE CHILDHOOD MALNUTRITION

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree

of

Master of Medicine in the branch of Paediatrics

Johannesburg 2010

Declaration

I, Tim De Maayer declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics.

Signature

14th Day of May 2010

To my parents,

Peter De Maayer

&

Miek Mertens

Publications and presentations arising from this study

"The impact of HIV on severe childhood malnutrition", (oral presentation). 2nd Priorities in Child Health Conference, Johannesburg, 5 December 2008.

"Severe childhood malnutrition in a high HIV and tuberculosis prevalence African setting". Poster accepted for presentation, International Paediatric Association Conference, Johannesburg, August 2010.

Abstract

Aim:

Case fatality rates for child severe malnutrition have remained high globally and in South Africa. It has been postulated that much of this excess mortality is due to HIV infection. This study sought to examine case fatality rates in children with and without HIV infection, and with different forms of malnutrition.

Methods:

A prospective, observational study was undertaken at three academic hospitals in Johannesburg, South Africa. Severely malnourished children were identified and their anthropometric details, clinical features, laboratory findings and admission outcomes analysed. Nutritional status was categorised using the Wellcome and WHO classifications. All children had their HIV status established.

Results:

The case fatality rate in 113 severely malnourished children was 11.5%. Fifty one percent of children were HIV infected. Most (44%) of children had kwashiorkor, with 26% having marasmus and 20% classified as marasmic kwashiorkor. HIV positive children were significantly more likely to die than negative children (19% vs 3.6%, OR 6.2, 95% CI 1.2–59, p=0.02). Marasmic children were more likely to have HIV than those with kwashiorkor or marasmic kwashiorkor (83% vs 33%, OR 9.7, 95% CI 3.5–29.1, p< 0.001). Half (51%) of all HIV negative children whose mother's status was known had an HIV positive mother. TB was suspected and treated in 24% of children, although confirmed in only 19% of these. Factors associated with an increased mortality included hypothermia (OR 9.7), hypoglycaemia (OR 9.7), shock (OR 7.2), thrombocytopaenia (OR 5.7), raised INR (OR 9.8) and the intravenous administration of fresh frozen plasma or packed red blood cells (OR 9.7 and 7.8 respectively).

Conclusion:

The HIV pandemic has altered the face of malnutrition in the study setting. Case fatality rates remain unacceptably high in HIV positive malnourished children. Specific guidelines for the management of severe malnutrition in HIV positive children and improved tuberculosis, growth monitoring and growth promotion programmes could reduce this impact.

Acknowledgements

I wish to thank my supervisor, Prof Haroon Saloojee, whose encouragement, knowledge and experience were instrumental in reaching the stage when this document will be printed. His dedication and time despite countless other commitments are much appreciated.

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1. Background

1.1. Setting the scene

Childhood malnutrition and more specifically, undernutrition, is a public health problem as old as time. Little is known about the prevalence and mortality of severe malnutrition before the 19th century, perhaps because it was so common that it was seen as a normal part of life. Despite the enormous progress made by humanity since then, malnutrition remains rife in many parts of the world.[1]

Globally, this disease remains an important cause of death in children under five years of age. Recently, mathematical models have estimated that more than half of all deaths in children worldwide are related to undernutrition (defined as weight one or more standard deviations below expected for that age when compared to an international reference population).[2] In this context, poor nutrition has been shown to increase a child's risk of dying due to diarrhoea, pneumonia, measles, malaria and other infectious diseases. Being underweight and the associated micronutrient deficiencies affect the host's immune and non-immune defences, and this makes the child more likely to suffer life threatening infections.

Apart from undernutrition contributing to such a large proportion of deaths in children under five, severe malnutrition is a well recognised main cause of death in children in this age group. The disease carries a high (20-60%) case fatality rate in some settings and has been a focus of several World Health Organization (WHO) initiatives to improve its prognosis.[3, 4] In South Africa, the Medical Research Council carried out studies in 2000 to estimate the burden of disease profile for different age groups. Severe malnutrition ranked as the number five cause of death for all children under five years of age.[5] In rural areas the problem is even larger, as is shown in the annual census data from Agincourt in Limpopo, where malnutrition remains among the top four causes of death in the same age group.[6]

The seriousness of the situation in South Africa has recently been highlighted by the 2005 National Food Consumption Survey. While stunting (height for age greater than two standard deviations below expected) remains the most prevalent form of undernutrition, occurring in 23.4% of children aged one to three years, the rates of underweight (weight for age greater than two standard deviations below the mean) and wasting (weight for height greater than two standard deviations below the mean) are also unacceptably high occurring in 11% and 5.2% respectively of all South African children aged one to three years. Although the survey found that most growth parameters measured had improved slightly from those found in the 1999 National Food Consumption Survey, it is of particular concern that there has been a statistically significant increase in the prevalence of wasting and severe wasting (weight for height greater than three standard deviations below the mean) in urban areas. The authors suggest that an accelerated rate of urbanisation may be partially responsible but assert that the impact of the Human Immunodeficiency Virus (HIV) pandemic must be examined closely.[7]

Malnutrition has been highlighted by the United Nation's Millennium Development Goal (MDG) initiative.[8] This initiative has set eight broad goals with 2015 as a target date, hoping to bring improvement in key areas in health, education, environmental concerns and social development. The first MDG is to halve the amount of people suffering from hunger and poverty between 1990 and the year 2015. Similarly, the fourth MDG is to reduce under-five mortality by two thirds in the same time period.[8] The United Nations 2008 MDG progress report describes how rising food prices are one of the major factors limiting the global ability to achieve the first goal. Sub-Saharan Africa is identified as having made little or no progress towards goal 4 - reducing child mortality.[9]

In South Africa, a double burden of malnutrition has been described: there is obesity which leads to diseases such as diabetes mellitus and hypertension in adults on the one extreme, and there exists a large burden of undernutrition on the other extreme.[10]

1.2. Classification of malnutrition

Many different classifications of severe malnutrition have been used.[11] Perhaps the most commonly used is the WHO classification, which primarily uses wasting as an indicator of severe disease.[12, 13] It includes children with a weight for height z-score of -3 or less, a mid-upper arm circumference of less than 11.5 cm or the clinical criteria of severe visible wasting or bipedal oedema. In South Africa, most health centres still prefer to use the Wellcome classification.[14] In this system, marasmus, kwashiorkor, and marasmic kwashiorkor may be classed as severe malnutrition. Table 1.1 illustrates this classification. In practice, the WHO definition is slightly broader, and more children will be identified as having severe malnutrition if one uses this definition. While the management of these additional patients classified as severe malnutrition using the WHO definition carries little risk and is likely to be beneficial, resources and economic constraints may discourage the use of a less discriminate definition.

Table 1.1 The Wellcome classification of severe malnutrition[14]

	No oedema	**Oedema**
60-80% expected weight for age	Underweight	Kwashiorkor
<60% expected weight for age	Marasmus	Marasmic kwashiorkor

1.3. HIV/AIDS

The HIV pandemic is thought to be largely responsible for the halted decline in malnutrition rates in South/ern Africa.[7] Sanitation and household food security have improved in urban South African settings [15] and secondary malnutrition (owing to a defined medical or surgical condition) may be obscuring an absolute decline of children with primary malnutrition. This is similar to patterns described in the West Indies in the last decade of the 20th century.[16] Over the last two decades, African studies have described prevalence rates of HIV infection in severely malnourished

children ranging from 13.8% to 48.6%.[17-19] Although limited data are available about the situation in South Africa, HIV is likely to be a significant contributor in view of the infection's high prevalence here.[20]

Failure to thrive is a well described feature of paediatric HIV infection, and due to a vicious cycle of immune dysfunction, infections and malnutrition, these children are vulnerable to both the oedematous and non oedematous forms of the disease.[21] Nevertheless, traditional risk factors for developing severe malnutrition such as poor social circumstances and food insecurity still play an important role.[22]

Despite progress made in the Prevention of Mother to Child Transmission (PMTCT) of HIV programme, a large number of South African HIV positive infants remain undiagnosed until they are symptomatic. Many infants are already severely malnourished by the time they first present to the health services. They are at a high risk of dying from overwhelming infections in the course of their first hospital admission.[23] Additionally, the recent CHER study in South Africa showed that all infants with HIV should be started on highly active antiretroviral therapy (HAART), as soon as possible after diagnosis and that this reduces mortality significantly.[24] It is clear that South Africa and other African countries need to strengthen their PMTCT and infant diagnosis and treatment programmes if they are to stand a chance to reduce infant and under-five mortality and severe malnutrition rates.

1.4. Case fatality rates

In 1996, a seminal literature review was published by Ashworth in the Bulletin of the World Health Organization on the persistently high mortality rates seen across the world.[25] Mortality rates remained at 20-30% for all children admitted with severe malnutrition, but were even higher (50-60% in some places) for the oedematous forms of malnutrition.[25] Inadequate case management and conflicting guidelines were identified as potential causes for this high case fatality and hence the WHO guidelines were conceived.[3, 4]

The WHO manuals are aimed at doctors and primary health care workers and provide mainly evidence based principles and guidelines to adequately treat severely malnourished children. The original aim was to decrease the case fatality rates of severe malnutrition to below five percent. This target has been achieved in several settings, although these settings were mainly dealing with acute starvation situations or had a low HIV prevalence.[26] The WHO guidelines were tested in two rural settings in South Africa and although they were able to decrease mortality to 18% at both sites, the five percent target remained elusive.[27, 28] It was hypothesised that the excess mortality was largely due to HIV.

This was shown to be the case recently in a prospective cohort study from Malawi where children with severe malnutrition were followed up for four months after discharge from hospital. The observed mortality rate was 35.4% in the HIV positive children, versus 10.4% in HIV uninfected children ($p<0.001$). The highest mortality rate (40%) was seen in children with a CD4 count of less than 20%.[29]

1.5. Direct causes of death

The common direct causes of death and poor outcome, and steps to prevent them, are addressed extensively in the WHO "10 steps" to manage severe malnutrition guidelines.[3] These include the prevention and treatment of hypoglycaemia, hypothermia, dehydration, electrolyte abnormalities and infections. They also expand on the treatment of shock, septic shock and severe anaemia while carefully avoiding fluid overload in these acutely ill patients. Another point that is emphasised is the provision of a somewhat calorie and protein restricted diet (F75) in the early days of admission, as it is thought that the child will be unable to cope with the extra metabolic stress of a richer diet.[25] While these are all well accepted and researched management principles, the "10 Steps" protocol is not widely practised in the hospitals participating in the current study. In these

Johannesburg hospitals, all severely malnourished children are managed by a team that is nevertheless experienced in the care of severely malnourished children and each child's care is supervised by paediatricians and dieticians.

1.6. Prognostic factors

In view of the high case fatality rate experienced, several studies have attempted to establish poor prognostic features. One of the first studies was done at Baragwanath Hospital in 1959, and its results are still often quoted on paediatric ward rounds in this hospital.[30] From these early observations, generations of students have been taught a mnemonic (WEEPJIPHHH) to help remember some of these features. "WEEPJIPHHH" stands for Weeping dermatitis, Enlarged liver (>4 cm), Eye ulcerations, Petechiae, Jaundice, Infection, Pallor, Hypoglycaemia, Hypothermia and Hypokalaemia. The prognostic validity of these findings in the present high HIV prevalence setting has not been tested, and it seems unlikely that they still carry the same implications as 50 years ago. Several more recent studies have looked at poor prognostic features since then, and although there is little consensus within them, the following feature frequently: severe dehydration, severe acidosis, electrolyte imbalances and the administration of intravenous infusions of blood or fluid.[31-33] In particular, Maitland and colleagues published a large, retrospective data set which showed that the WHO danger signs (lethargy, hypothermia and hypoglycaemia), brady cardia, prolonged capillary refill time > 2 sec, a weak pulse and impaired level of consciousness were the most significant predictors of death in their multivariate analysis.[31]

1.7. Infections and malnutrition

Infections are an important part of the vicious circle in severe childhood malnutrition.[34] While this review has already described the relationship between HIV and malnutrition (see section 1.3), there are several other infections which are pertinent. Concurrent with the HIV pandemic, tuberculosis (TB) has become a more frequently found illness in children, owing to both increased

exposure from infected adults and the immune paresis present in children infected with HIV.[35] While TB has traditionally been very difficult to diagnose in children, it is even more challenging in children with HIV and/or malnutrition, with both diseases diminishing the tuberculin skin test response.[36, 37] In addition, distinguishing TB disease from TB infection is difficult and often based on clinical signs and symptoms which overlap with those of HIV. It is therefore of paramount importance that basics such as contact tracing and isoniazid prophylaxis are practised routinely.

While TB and HIV can both cause childhood malnutrition, many other infections are often as an indirect result of malnutrition. The immune dysfunction that results from poor nutrition has been studied extensively over the last 50 years.[38] In children with severe malnutrition, high prevalences of bacteraemia (12-22%), urinary tract infections (8-35%), gastroenteritis (27-71%), pneumonia (26-38%) and nosocomial infections (21-49%) have been described.[39-45] These infections are in fact so common that the WHO guidelines recommend the routine administration of broad spectrum antibiotics to all severely malnourished children.

1.8 Justification for this study

This research project is unique primarily because of its setting: the outcome of severe malnutrition has not been studied in a resource privileged but high HIV prevalence setting such as the academic hospitals in Gauteng. The project also explores the relationship of this outcome to the type of malnutrition (kwashiorkor or marasmus) and HIV status.

Other aims include the opportunity to look at the prevalence of infections in malnourished children infected with HIV, and where possible to look for direct causes of death. Additionally, this research provides an opportunity to examine poor prognostic factors for this group of children.

2. Methods:

2.1. Definitions

Children were defined as having severe malnutrition if they fulfilled the World Health Organization (WHO) or the Wellcome classification criteria. (See section 1.2 and Table 1.1)

2.2. Study hypothesis

Severely malnourished children who are infected by HIV have a poorer outcome than their HIV negative counterparts, and the WHO target case fatality rate of less than 5% may be unrealistic in a high HIV prevalence setting.

2.3. Objectives

Primary objective:

- To determine in-hospital case fatality rates for children with severe malnutrition admitted to academic hospitals in Johannesburg, and compare the outcomes of HIV positive and negative children

Secondary objectives:

- To compare case fatality rates in different types of malnutrition: kwashiorkor, marasmus and marasmic kwashiorkor
- To identify poor prognostic factors in the different malnutrition groups
- To establish direct causes of death where possible
- To determine the prevalence of bacterial infections in this population

2.4. Study design

A prospective, observational study design was used.

2.5. Study setting

The study was conducted at three academic hospitals in Johannesburg: the Charlotte Maxeke Johannesburg Academic Hospital (formerly Johannesburg General Hospital), the Chris Hani Baragwanath Hospital and the Rahima Moosa Mother and Child Hospital (formerly Coronation Hospital).

2.6. Study sample

An attempt was made to enrol all children admitted to any of the above hospitals between 4 September and 30 November 2008. Inclusion criteria were an age of less than 60 months and a diagnosis of severe malnutrition.

An ideal sample size was calculated using an estimated case fatality rate of 5% in HIV negative children and 15% in HIV positives, assuming that 50% of patients with severe malnutrition would be HIV positive. Using Epi Info 3.4.1 (CDC, Georgia, USA), a sample size of 318 patients would be needed to show a statistical difference in mortality of 10%, with 95% confidence (p-value <0.05) and a study power of 80%. However, in view of the time limit for this projects' data gathering, it was decided to enrol as many patients as possible in the available time, and continue even if the ideal sample size was not achieved.

2.7. Measuring tools

2.7.1. Identification and enrolment

Paediatric registrars who worked in any of the three hospitals' admission wards were asked to identify potential participants on hospital admission, and to get informed consent from the child's caregiver for enrolment in the study. This was done to maximise enrolment and avoid the difficulties in obtaining consent at a later stage (when the caregiver may no longer be present) or in case the child died soon after admission.

2.7.2. Measurements

The researcher visited each hospital at least twice a week to gather data on all newly and previously enrolled participants. The first weight recorded on hospital admission was used as a patient may have lost weight owing to resolution of oedema by the time the researcher visited them. Length was measured by the researcher with a foldable, measuring board on which the child could lie. Recumbent length was used unless the child was over the age of two years and able to stand. The measuring board was laid flat on the child's bed and straightened. The child was then placed on top with his or her head against the head piece of the board. The child's head was put in a neutral position and the length was read at the bottom of the feet to the nearest millimetre. Occipitofrontal head circumference and mid-upper arm circumference (MUAC) were measured by the researcher with a tape measure to the nearest millimetre. MUAC measurements can be used as a marker for wasting. Since this measurement changes little during the first few years of life, 11.5 cm has been used as a cut-off value for children between six months and five years.[12] Anyone who has a lower MUAC is likely to be severely wasted. Occipitofrontal diameter was measured extending the tape from the most prominent part of the occiput and across the forehead just above the glabella. Mid-upper arm circumference was measured at the midpoint between the acromium and the lateral epicondyle of the humerus. Both the measurements obtained from the patient record (as done by the admitting doctor, usually by means of a tape measure) and those by the researcher were captured and compared. The researcher's measurements (or the ward doctors' measurements if not measured by the researcher) were converted to z-scores using the WHO Anthro software (available from http://www.who.int/childgrowth/),[46] using the WHO reference values.[47]

2.7.3. Study data sheet

A detailed, 155-item study data sheet was completed by the researcher for each participant (Appendix A). The data sheet included data about anthropometrics, HIV status, presenting complaints, additional history, vital signs and examination findings, laboratory results, patient management and the outcome of the admission. The history was primarily obtained from the file, but if the caregiver was present at the time the researcher was visiting the child, the researcher verified information and asked further details. In the majority of cases this was not possible. The information in the file was not always complete. Data on feeding practices and social history especially were scant, and little inference could be drawn from these as a result. Examination findings were also obtained from the file and then verified by a brief examination conducted by the researcher.

2.7.4 Definitions

Shock was defined clinically as a prolonged capillary refill time (>3 sec), cold peripheries or low blood pressure for age. Hypothermia was defined as a core body temperature of less than 35°C. Respiratory distress was defined as tachypnoea (for age), alar flaring, chest recessions or the use of accessory muscles. Lymphadenopathy was defined as lymph nodes larger than 0.5 cm. Staining the eyes with fluorescein to identify corneal ulcers was done by the attending doctors.

Laboratory results were obtained from the various National Health Laboratory Services (NHLS) computer systems at each of the hospitals. Urinary tract infection was defined as the presence of more than 10^6 organisms/ml of fresh urine, more than 10^3 per ml of suprapubically aspirated urine, or a positive urine culture (excluding skin contaminants).

2.7.5 Outcomes

The researcher briefly saw each child on subsequent visits to identify any further changes in the child's condition and management. The outcome for each child was captured as one of three

categories: discharged, died, or transferred to a recuperative care hospital (Selby Park Hospital) when stable. In cases of death, the immediate cause of death and the Child Health Problem Identification Programme (CHIP) data form was captured. While it was not possible in this study to identify the direct cause of death in all patients, an attempt was made to identify this from examining the ward notes, death certificates and, where available, Child Health Problem Identification Programme (CHIP) forms. Unfortunately, only one of the three hospitals was using the CHIP audit system at the time of the study. Selby Park Hospital was visited to examine whether any further complications or death occurred to children while admitted there. The results of cultures for *Mycobacterium tuberculosis* species from blood and sputum were reviewed at a later date.

2.8. Patient management

Patients were managed by the attending ward doctors as per the existing ward protocols or guidelines. In this setting, the patient is seen daily by a medical intern or medical officer as well as a paediatric registrar. He or she in turn is guided by a specialist paediatrician. Although no written protocols are followed for managing severe malnutrition, broad management principles are similar to those set out in the WHO's "10 step" protocol. The areas where the local study site management differed significantly from the WHO guidelines included the lack of provision of F75 and F100 feeds and mineral supplements. Criteria for blood transfusions and intravenous fluids are also not as strict as in the WHO manual, and these decisions are made by the attending registrars and consultants.

Routine investigations done on all severely malnourished children included: a full blood count, urea and electrolytes, liver function test, clotting profile (INR), blood culture, C-reactive protein and a urine dipstix and culture. HIV status was confirmed in children under 18 months using a HIV polymerase chain reaction test (PCR) or by use of an HIV ELISA in children over 18 months of age. Induced sputum or gastric washings for TB microscopy and culture were performed when TB was suspected. Analysis of these specimens was done by the National Health Laboratory Service that served the three hospitals. Discharge criteria and down-referral criteria for patients varied, but

generally patients were expected to show two consecutive weight gains before discharge and had to be stable and have lost all oedema (if present) before down-referral.

2.9. Data capture and statistical analysis

A database was designed in Microsoft Office Access 2007 (Microsoft, Seattle, USA) by the researcher. Data were entered and data cleaning was also done using this software. Data analysis was done using SPSS 15 (SPSS Inc, Chicago, USA) and Intercooled Stata 7.0 (Stata Corp., College Station, Texas, USA). Graphs were produced using SPSS 15 and Microsoft Office Excel 2007 (Microsoft, Seattle, USA). Comparison of means was done using the student's t-test for parametric data, and bivariate analysis using the chi-square test. Comparison of medians for non-parametric data was done using the Mann-Whitney test, and survival analysis using the log rank test. Visual inspection of histograms, and Shapiro-Wilk tests confirmed which continuous variables followed a normal distribution. Odds ratios (OR), standard deviations (SD), interquartile ranges (IQR) and 95% confidence intervals (95% CI) are specified where applicable. A p-value < 0.05 was considered statistically significant.

2.10. Ethical considerations

Data capture sheets did not contain names, hospital numbers or any other information that could identify the participants. A unique study number was used as a key to link the data capture sheets to the participant's information. Ethical approval was obtained from the Committee for Research in Human Subjects at the University of the Witwatersrand (Medical) (Protocol number M080809) (Appendix B). Permission was also obtained from the Gauteng Department of Health and the medical superintendents at the various hospitals (Appendix C).

2.11. Finance:

Funding was received from the Faculty of Health Sciences' Faculty Research Committee.

3. Results

3.1. General characteristics

One hundred and fifteen children were enrolled. Two children were later excluded. Both were initially considered to have kwashiorkor, but the first child was reclassified as a nephrotic syndrome and the second as an HIV associated nephropathy.

Of the remaining 113 patients, 55 (49%) were female. The patient contribution of the various hospitals was as follows: 24 (21%) from Charlotte Maxeke Johannesburg Academic Hospital, 44 (39%) from Rahima Moosa Mother and Child Hospital and 45 (40%) from Chris Hani Baragwanath Hospital.

The median age of the children was 10 months (interquartile range [IQR] 5-17 months), with a range of 1 to 34 months (Figure 3.1). Fifty-eight children tested HIV positive (51%), while 55 were HIV negative (49%). Within the HIV negative group, 19 (35%) children had a HIV positive mother, 18 (33%) a HIV negative mother, and in 18 (33%) cases the mother's HIV status was unknown.

Classification of Malnutrition

All patients who fulfilled the Wellcome criteria also met the WHO criteria. Every child that qualified according to the WHO criteria did so with significant wasting (weight for length z-score less than -3), a MUAC of less than 11.5cm or bipedal oedema (see figure 3.2). Eight children (7%) who met the WHO definition for severe malnutrition did not meet the Wellcome classification criteria. Four of the eight had bipedal oedema but their weight was more than 80% of expected weight for age, while a further four were severely wasted (weight for length Z-score < -3), but their weight was not less than 60% of expected for their age (see Table 3.1). For further analysis, the first four children have been reclassified as having kwashiorkor, the latter four as marasmic.

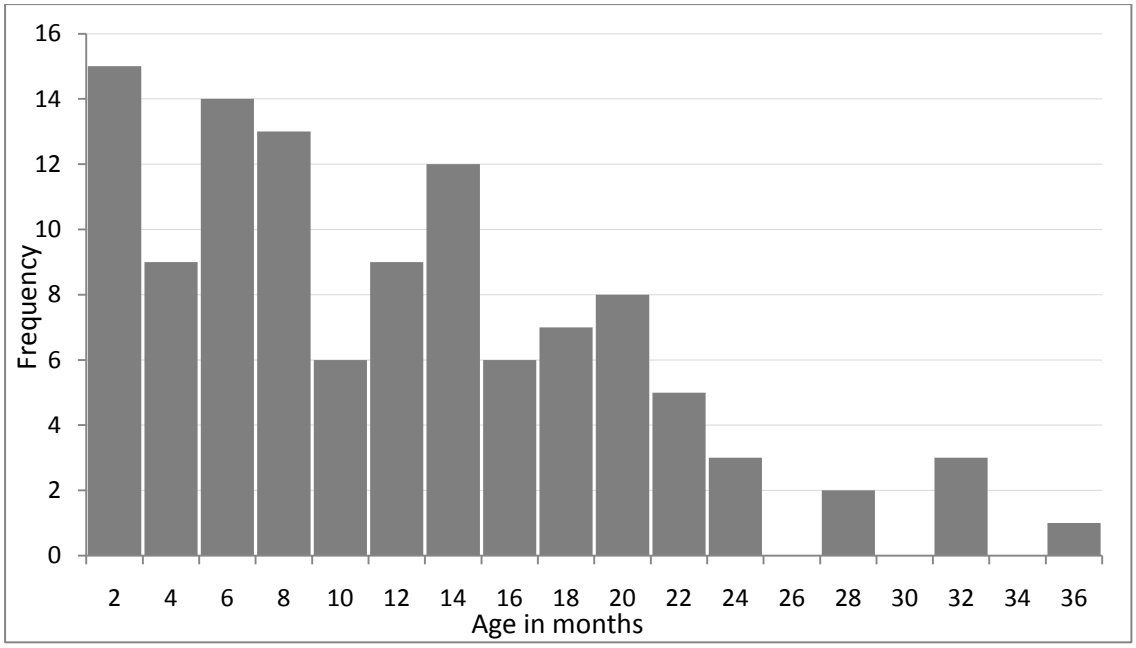

Figure 3.1 Age distribution in months of severely malnourished children (N=113)

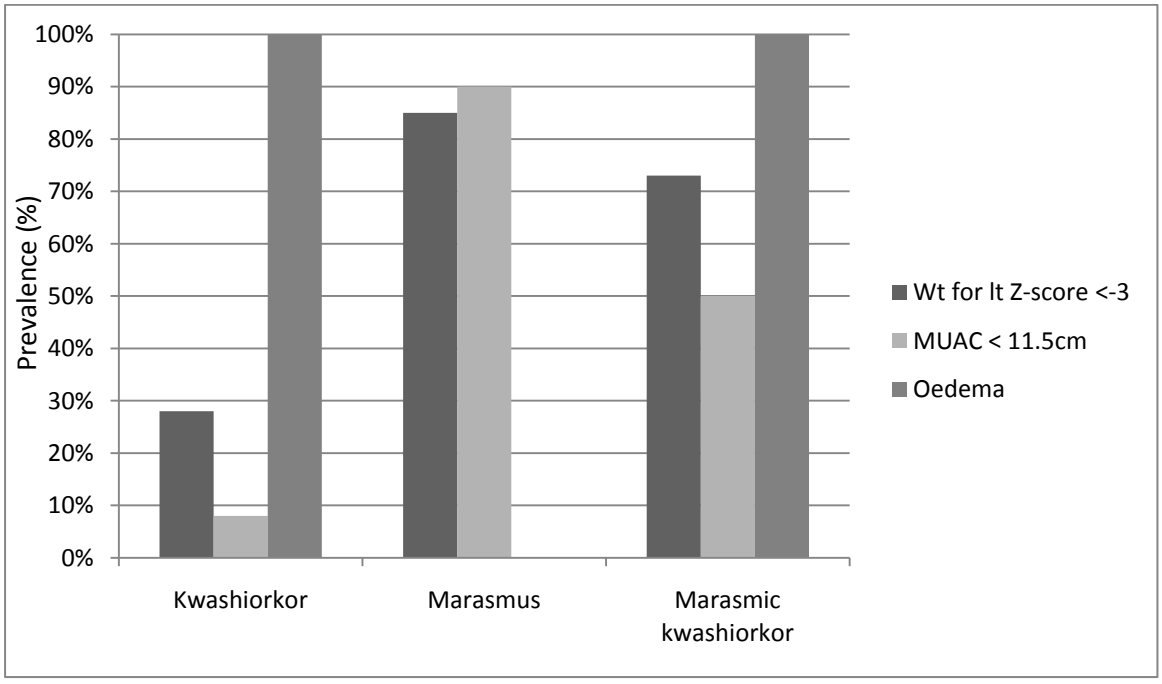

Figure 3.2 Prevalence of WHO criteria for severe malnutrition in different Wellcome classes.

(N=113)

Table 3.1 WHO criteria for severe malnutrition compared to other signs/criteria (N=113)

	Weight for Age Z-score < -3	Weight for length Z-score < -3	MUAC < 11.5 cm	Severe visible wasting	Bilateral pedal oedema
Oedema only (n= 4)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)
Wasting only (n= 4)	3 (75%)	4 (100%)	3 (75%)	4 (100%)	0 (0%)
Marasmus (n= 37)	37 (100%)	31 (84%)	34 (92%)	34 (92%)	0 (0%)
Kwashiorkor (n= 46)	21 (46%)	14 (30%)	4 (9%)	3 (7%)	46 (100%)
Marasmic-kwashiorkor (n=22)	22 (100%)	16 (73%)	11 (50%)	13 (59%)	22 (100%)

Wasting defined as weight for length Z-score less than -3.
Kwashiorkor and Marasmic Kwashiorkor defined using Wellcome classification
MUAC= mid upper arm circumference

Following the reclassification, there were 50 (44%) children with kwashiorkor, 41 (36%) with marasmus, and 22 (20%) with marasmic kwashiorkor.

Marasmic children were more likely to be HIV positive than those with kwashiorkor or marasmic kwashiorkor (83% vs. 33%, Odds ratio [OR] 9.7, 95% confidence interval [95% CI] 3.5–29.1, p< 0.001), while children with kwashiorkor were less likely to be HIV positive compared to the others (32% vs 67%, OR 0.24, 95% CI 0.1–0.6, p< 0.001) (Table 3.2).

Table 3.2 HIV infection rates in different types of malnutrition (N=113).

	Total	HIV positive n (%) N=58	HIV negative n (%) N=55	Odds ratio	95% CI	p value
Kwashiorkor	50	16 (32)	34 (68)	0.24	0.1 – 0.6	< 0.001
Marasmus	41	34 (83)	7 (17)	9.7	3.5 – 29.1	< 0.001
Marasmic kwashiorkor	22	8 (36)	14 (64)	0.47	0.16 – 1.3	0.15

Children with kwashiorkor were older than those with marasmus and marasmic kwashiorkor (Medians: 15.0 vs. 6.0 and 10.5 months, p< 0.001 and p= 0.04 respectively). HIV positive children were younger than HIV negative children, although the difference was not significant (Median age 8 vs. 12 months, p= 0.15). Fifteen infants (13%) were aged less than three months: two (13%) had marasmic kwashiorkor, three (20%) had kwashiorkor and 10 (67%) had marasmus. Eleven (73%) of these young infants were HIV positive. This higher prevalence of HIV in severely malnourished infants under three months was not statistically significant (OR 2.98, 95% CI 0.8-14, p=0.07).

Anthropometrics

One hundred and one (89%) of the children's lengths and head circumferences were re-measured by the researcher, following admission. This revealed discrepancies with the measurements in the child's hospital file, especially with regard to length. On average, the lengths differed by 2.74 cm (range 0–13 cm) and the head circumference by 0.71 cm (range 0–3 cm). For the length, the measurements differed by more than 2.5 cm in 43% of cases. For the majority of these (84%), the researcher's value was higher than that recorded in the file.

Fifty two children (48%) had a mid-upper arm circumference (MUAC) of less than 11.5 cm. A MUAC of less than 11.5 cm was compared to a WHO classification of severe wasting (weight for length Z-score < -3). The sensitivity and specificity of a MUAC of < 11.5 cm for severe wasting was 74% and 75% respectively. This translates to a positive likelihood ratio of 2.91 and a negative likelihood ratio of 0.34.

3.2. History

Presenting complaint

The three commonest presenting complaints were coughing (52%), diarrhoea (52%) and fever (29%). A history of coughing was more common in the wasted or marasmic group of children than in

those with kwashiorkor (OR 3.34, 95% CI 1.3–8.9, p= 0.01). Chronic cough (more than 14 days) showed a similar trend, but this was not statistically significant (OR 2.18, 95% CI: 0.6–9.2, p= 0.24). Fever was also more common in marasmic children (OR 3.45, 95% CI: 1.3-9.8, p= 0.01) (Table 3.3).

Table 3.3 Presenting complaints according to type of malnutrition (N=113).

	Total	Kwashiorkor n (%) N=50	Marasmus n (%) N=41	Odds ratio	95% CI	p value
Diarrhoea	47	25 (50)	22 (54)	0.86	0.4–2.1	0.83
Persistent diarrhoea	7	5 (10)	2 (5)	2.17	0.3–24	0.45
Cough	50	21 (42)	29 (71)	0.30	0.1–0.8	0.01
Chronic cough	13	5 (10)	8 (20)	0.46	0.1–1.8	0.24
Fever	29	10 (20)	19 (46)	0.29	0.1–0.8	0.01

Past medical history

Almost half the children (46%) had previously been admitted to a hospital. This was more common in the HIV positive group (62% vs. 29%, OR 4.0, 95% CI 1.7–9.5, p< 0.001). The caregivers of 13 (36%) of the HIV positive children who had been previously admitted claimed that this was the first time their child was diagnosed with HIV.

The majority (86%) of children whose immunisation status was known were up to date with their immunisations. Only 2 children (2%) had never been immunised, while 11 (12%) were missing one or more immunisations.

Although 17 children (15%) had a close tuberculosis contact when asked about this on history, none of them were started on isoniazid prophylaxis prior to admission, as is recommended in the national tuberculosis guidelines. Five of these 17 children (29%) were started on TB treatment during this admission; all of the others commenced TB prophylaxis.

Breastfeeding

Information on breastfeeding data was available for 82 children (73%). This data is summarised in table 3.4. Only 4% of children were currently breastfed, with more than half (56%) never breastfed. There was a trend towards HIV negative children with a negative mother being more likely to have been breastfed (previously or currently) (OR 5.4, 95% CI 0.9-35.0, p=0.06).

Table 3.4 Child's breastfeeding status according to child and mother's HIV infection status (N=82)

	Currently breastfeeding n (%)	**Previously breastfed n (%)**	**Never breastfed n (%)**
Child HIV positive, mother positive	2 (4)	17 (37)	27 (59)
Child HIV negative, mother positive	0 (0)	4 (25)	12 (75)
Child HIV negative, mother negative	1 (7)	8 (57)	5 (36)
Child HIV negative, mother's status unknown	0 (0)	4 (67)	2 (33)
Total	3 (4)	33 (40)	46 (56)

3.3 Clinical features

Clinical features commonly found in malnourished children are summarised in table 3.5 and 3.6. Of note is the frequent finding of dehydration and shock, and of signs associated with HIV disease: hepatosplenomegaly, lymphadenopathy and oral candidiasis. Children with HIV were significantly more likely to have hepatomegaly (OR 3.3, 95% CI 1.1-11, p=0.03), lymphadenopathy (OR 6.4, 95% CI 2.4-16, p<0.001), oral candidiasis (OR 2.4, 95% CI 1.0-5.7, p=0.05), respiratory distress (OR 4.1, 95% CI 1.5-12, p= 0.002) and splenomegaly (OR 4.5, 95% CI 1.1-26, p=0.02).

Table 3.5 Clinical signs classified by Wellcome classification status (N=113)

	Total n (%) N= 113	Kwashiorkor n (%) N= 50	Marasmus n (%) N= 41	Marasmic kwashiorkor n (%) N= 22	p-value
Hepatomegaly	92 (81)	41 (82)	34 (83)	17 (77)	0.85
Lymphadenopathy	72 (64)	28 (56)	31 (76)	13 (59)	0.14
Pallor	61 (54)	25 (50)	22 (54)	14 (64)	0.57
Dehydration	60 (53)	22 (44)	24 (59)	14 (64)	0.21
Oral candidiasis	40 (35)	10 (20)	19 (46)	11 (50)	0.01
Respiratory distress	32 (28)	9 (18)	20 (49)	3 (14)	<0.01
Shock	21 (19)	10 (20)	7 (17)	4 (18)	0.94
Weeping dermatitis	7 (6)	5 (10)	1 (2)	1 (5)	0.31
Splenomegaly	15 (13)	3 (6)	9 (22)	3 (14)	0.08
Conjunctival ulceration	8 (7)	6 (12)	0 (0)	2 (9)	0.08
Hypothermia (<35˚C)	6 (5)	3 (6)	3 (7)	0 (0)	0.45
Bruising or petechiae	3 (3)	3 (6)	0 (0)	0 (0)	*
Jaundice	0 (0)	0 (0)	0 (0)	0 (0)	*

* p value could not be calculated as two or more cells= 0

Table 3.6 Clinical signs classified by HIV status (N=113)

	Total n (%) N= 113	HIV positive n (%) N= 58	HIV negative n (%) N= 55	Odds ratio	95% CI	p value
Hepatomegaly	92 (81)	52 (90)	40 (73)	**3.3**	**1.1 - 11**	**0.03**
Lymphadenopathy	72 (64)	48 (83)	24 (44)	**6.2**	**2.4 - 16**	**<0.01**
Pallor	61 (54)	30 (52)	31 (56)	0.8	0.4 – 1.9	0.71
Dehydration	60 (53)	36 (62)	24 (44)	2.1	0.9 – 4.8	0.06
Oral candidiasis	40 (35)	26 (45)	14 (25)	**2.4**	**1.0 – 5.7**	**0.05**
Respiratory distress	32 (28)	24 (41)	8 (14)	**4.1**	**1.5 - 12**	**<0.01**
Shock	21 (19)	13 (22)	8 (15)	1.7	0.6 – 5.2	0.34
Splenomegaly	15 (13)	12 (21)	3 (5)	**4.5**	**1.1 - 26**	**0.02**
Conjunctival ulceration	8 (7)	4 (7)	4 (7)	0.9	0.2 – 5.4	0.90
Weeping dermatitis	7 (6)	1 (2)	6 (11)	0.1	0.00 – 1.3	0.06
Hypothermia (<35˚C)	6 (5)	2 (3)	4 (7)	0.5	0.04 – 3.4	0.43
Bruising or petechiae	3 (3)	1 (2)	2 (4)	0.5	0.01 – 9.2	0.61
Jaundice	0 (0)	0 (0)	0 (0)	*	*	*

* OR, 95% CI and p value not calculated as both cells= 0

3.4 Laboratory results

Although the mean haemoglobin was low (8.9 g/dl) on admission, only one child had an absolute indication for blood transfusion according to the WHO guidelines (haemoglobin of ≤ 4 g/dl). An additional 10 children may have qualified if they showed signs of cardiac decompensation as a result of the anaemia (haemoglobin of 4 to 6 g/dl). Twenty five (22%) children received one or more blood transfusions, but not all of these were given on the basis of the admission haemoglobin result: some were transfused on the basis of a later result, which was not captured by the researcher. Eight children (7%) had a platelet count of less than 100,000/µl.

Hypokalaemia (potassium < 3.0 mmol/l) occurred in 32% of patients, while the bicarbonate value was less than 17 mmol/l in 52%. Elevated C-reactive protein levels (>10 mg/l) were seen in two thirds of children (67%), with 47 (44%) having a level over 40 mg/l. Albumin levels were checked on all 72 children with oedematous malnutrition, and 22 of 41 (54%) of the marasmic children. Although there was a significantly lower albumin in the group with oedema (23.2 versus 29.4 g/l, p< 0.001), there was a significant overlap between the two groups. The range of albumin levels in the oedematous group was 9 to 38 g/l, while in the marasmic groups values ranged between 19 and 40 g/l. Eleven (10%) of patients had an INR of greater than 1.7 (table 3.7).

Table 3.7 Laboratory investigations classified by Wellcome classification status (N=113)

	Total n/N (%)	**Kwashiorkor n/N (%)**	**Marasmus n/N (%)**	**Marasmic kwashiorkor n/N (%)**
Haemoglobin < 6 g/dl	11/113 (10)	4/50 (8)	5/41 (12)	2/22 (9)
Platelets < 100,000/µl	8/113 (7)	3/50 (6)	3/41 (7)	2/22 (9)
Potassium < 3,0 mmol/l	36/113 (32)	18 /50(36)	9/41 (22)	9/22 (41)
Bicarbonate < 17 mmol/l	59/112 (53)	22 /49(45)	23/41 (56)	14/22 (64)
CRP > 10 mg/l	72/108 (67)	35/49 (71)	27/40 (68)	10/19 (53)
Albumin < 30 g/dl	72/98 (73)	43/50 (86)	13/26 (50)	16/22 (73)
INR > 1.7	11/58 (19)	6/39 (15)	2/2 (100)	5/17 (29)
CD4 cell count < 20%	30/59 (51)	11/16 (69)	13/34 (38)	6/9 (67)
*** N varies because not all patients had each investigation.**				

3.5. Infections

Urinary tract infection

Thirty seven children (33%) had laboratory evidence of a urinary tract infection, based on the criteria explained in section 2.7.4. Nine (24%) of these failed to culture an organism or cultured contaminating organisms, but 76% of the samples cultured a likely organism. These included *Escherichia coli* (24)*, Klebsiella pneumoniae* (3) and *Proteus mirabilis* (1).

Septicaemia

A high incidence of bacteraemia (23%) also prevailed. Of all patients, 26 (23%) had at least one positive blood culture that was unlikely to be a skin contaminant (pseudo-bacteraemia). Organisms cultured are listed in table 3.8. *Escherichia coli* was the most commonly isolated organism. All four children that grew *Haemophilus influenzae* in their blood culture were fully immunised according to their Road to Health cards, and three of the four (75%) were HIV positive. The incidence of septicaemia did not differ significantly between children with marasmus, kwashiorkor or marasmic kwashiorkor (29%, 18% and 23% respectively). Similarly, HIV positive children had more positive blood cultures than HIV negative children (26% vs 20%), but once again this difference was non-significant.

Table 3.8 Organisms cultured from blood in children with severe acute malnutrition (N=113).

Organism	No.	Relative contribution (%)
Escherichia coli	7	27
Haemophilus influenzae	4	15
Streptococcus pneumoniae	4	15
Staphylococcus aureus	3	12
Klebsiella pneumoniae*	2	8
Streptococcus agalactiae	2	8
***Salmonella* species**	1	4
Enterococcus cloacae	1	4
Fungi (*Candida* species)	2	8
Total	**26**	**100**

* Both of these were extended spectrum beta-lactamase producing bacteria.

Tuberculosis

Pulmonary tuberculosis was a frequently suspected but seldom proven infection in malnourished children. Of 32 tuberculin skin tests whose result was recorded, only one was positive (PPD > 10mm). Gastric washings or induced sputa were done on 64 children, and yielded one positive microscopy for acid fast bacilli, and two positive *Tuberculosis mycobacterium* cultures. None of the six blood cultures for tuberculosis yielded any positive results. One child was suspected of having tuberculosis meningitis based on CT scan and lumbar puncture findings. This adds up to five children with "laboratory" evidence for tuberculosis, yet a total of 27 children were strongly suspected of having the disease on history, examination and chest X-rays, and were subsequently started on tuberculosis treatment. Marasmic and HIV positive children had TB treatment started more frequently, but the group with the highest rate of suspected tuberculosis was the HIV negative marasmic children: four of seven (57%) were started on treatment (table 3.9).

Table 3.9 TB treatment according to malnutrition type and HIV status (N= 113)

	Number treated (%)	p value
WELLCOME CLASSIFICATION		
Kwashiorkor (n= 50)	8 (16)	
Marasmus (n= 41)	16 (39)	
Marasmic kwashiorkor (n= 22)	3 (14)	0.02
HIV STATUS		
HIV positive (n= 58)	17 (29)	
HIV negative (n= 55)	10 (18)	0.19

Other infections

Other identified infections included one parvovirus B19 infection and one cytomegalovirus infection (both diagnosed using DNA polymerase chain reaction).

3.6. Patient management

All children were started on intravenous antibiotic therapy, 27 (24%) on anti-tuberculosis treatment, and 19 (17%) on anti-fungal treatment. All except two of the children started on antifungal treatment were started based on a clinical suspicion of oesophageal candidiasis. The two exceptions occurred in children where *Candida* species were cultured in their blood specimens.

Twenty five (22%) of children had one or more blood transfusions, while six (5%) received intravenous infusions of fresh frozen plasma.

Sixteen children (28% of HIV positive children) were on highly active antiretroviral therapy (HAART) in hospital, with 12 (75%) of them having been on the drugs prior to the current admission.

Treatment of malnutrition included the administration of vitamins and minerals, and the administration coverage rates are shown in table 3.10. The WHO guidelines recommending administration of measles vaccine to all children over six months of age who have not received it

previously, was poorly followed: of 25 children who qualified for this vaccine, only eight (32%) received it. Treatment with zinc, vitamin A and folate were particularly poor in marasmics compared to kwashiorkor (OR 0.06, 95% CI 0.01-0.28, p< 0.001; OR 0.02, 95% CI 0.00-0.14, p< 0.001 and OR 0.09, 95% CI 0.03-0.30, p< 0.001 respectively).

Table 3.10 Administration of vitamins and minerals in children with severe acute malnutrition (N=113).

	Total n (%) N= 113	**Kwashiorkor n (%) N= 50**	**Marasmus n (%) N= 41**	**Marasmic-kwashiorkor n (%) N= 22**
Potassium	75 (66)	46 (92)	12 (29)	17 (77)
Zinc	87 (77)	47 (94)	20 (49)	20 (91)
Vitamin A	71 (63)	47 (94)	9 (22)	15 (68)
Vitamin K	62 (55)	46 (92)	1 (2)	15 (68)
Multivitamins	69 (61)	32 (64)	24 (59)	13 (59)
Folate	78 (69)	44 (88)	16 (39)	18 (82)

3.7. Outcomes

Final outcome

Thirteen children (12%) died in hospital, 81 children (72%) were discharged directly from hospital, while 19 (17%) were transferred to Selby Park Hospital (a recuperation down-referral centre). All children transferred to Selby Park Hospital survived and were later discharged.

Mortality

Six deaths (46%) occurred within 48 hours of admission. Six of the nine (67%) HIV positive children who died were diagnosed for the first time during this admission.

Marasmus had a worse mortality than kwashiorkor, though this was not statistically significant (14% vs. 8%, OR 1.97, 95% CI 0.43–10.2, p= 0.34). The marasmic kwashiorkor group was closer to the marasmic group in terms of outcome (case fatality rate: 13.6%). HIV was a significant poor prognostic factor: 19% of positive children died compared to 3.6% of HIV negatives (OR 6.2, 95% CI

1.24–59, p= 0.016) (table 3.11). Survival analysis confirmed a statistical difference between HIV positive and negative children (p= 0.018) (figure 3.3).

Table 3.11 Mortality of severe malnutrition according to type of malnutrition and HIV status (N=113)

	Case fatality rate (%)	p value
WELLCOME CLASSIFICATION		
Kwashiorkor	4/50 (8)	
Marasmus	6/41 (15)	
Marasmic kwashiorkor	3/22 (14)	0.58
HIV STATUS		
HIV positive	11/58 (19)	
HIV negative	2/55 (3.6)	0.02

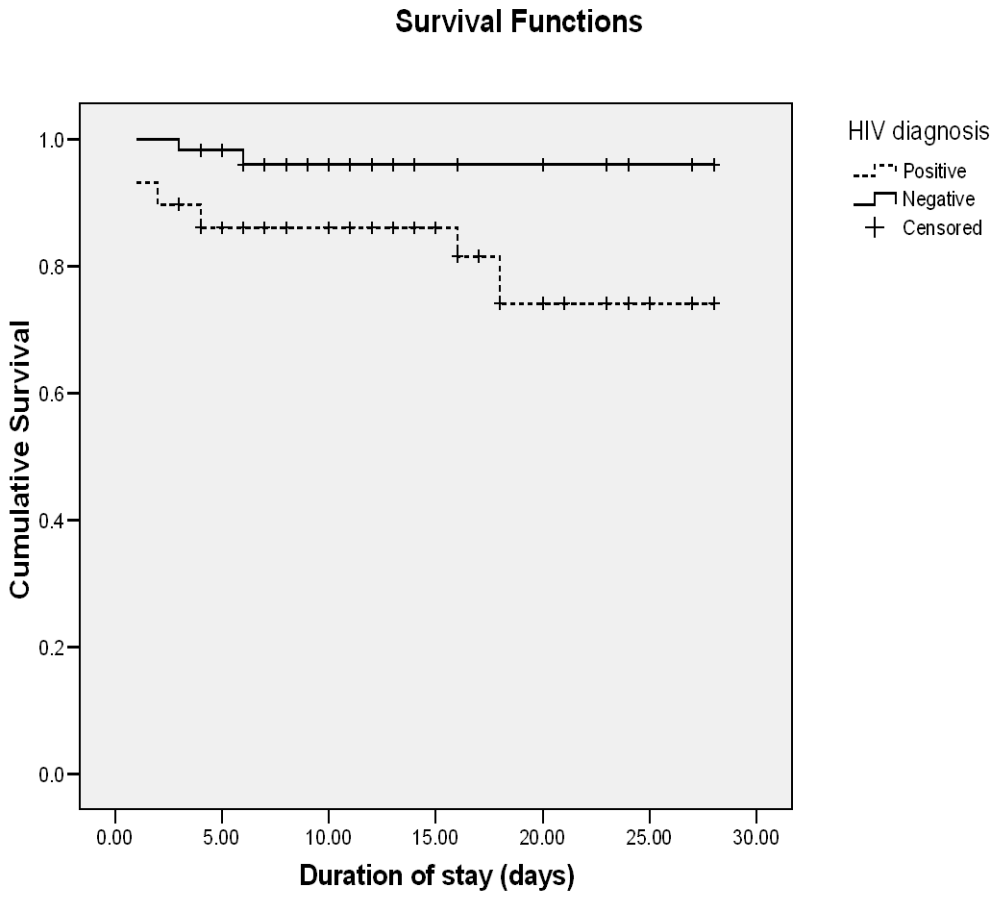

Figure 3.3 Survival of hospitalised severely malnourished children during the first four weeks after admission according to HIV status.

Duration of stay

The duration of stay averaged 12.7 days for the group of children who were discharged directly from their admitting hospital (Range 3 to 40 days, median 11 days). The total time spent in hospital by the Selby Park group of children (including the time spent at the admitting hospital) was 18.7 days on average (range 8 to 60 days, median 14 days). The total duration of stay of surviving patients did not differ between HIV positives and negatives (13.9 and 13.7 days respectively). For the 13 deaths, time from admission to death was a median of 3 days (IQR 1-6, range 1 to 30 days).

3.8. Poor prognostic factors

Several factors were tested against the likelihood of dying using univariate analysis. The factors that were considered for inclusion were chosen on evidence from previous publications on this subject (see section 1.6). Because of the low number of fatalities in the study, risk factors were tested for both all children and specifically for those with oedematous malnutrition (kwashiorkor and marasmic kwashiorkor).

Bruising or petechiae occurred in 13 patients, but none died. Jaundice did not occur in any patients, but it is probably a poor prognostic factor in view of the degree of liver dysfunction required to produce this sign. Some factors that indicate more severe disease were statistically significant: hypoglycaemia, a prolonged clotting time and corneal ulcerations are examples. Surprisingly, a low CD4 cell count (< 20%) was not a poor prognostic factor in this sample. Conversely, pallor, shock, and blood transfusions were significant risk factors. Further results are shown in table 3.12.

3.9. Causes of death

Septicaemia and septic shock were thought to be responsible for nine deaths (69%). Six children (67%) had positive blood cultures to support this finding. The responsible organisms were *Eschericia coli, Enterobacter cloacae,* extended beta-lactamase producing *Klebsiella pneumoniae,*

Staphylococcus aureus, and *Streptococcus pneumoniae*. Other suspected causes of death included pneumonia, cardiac failure secondary to fluid overload and immune reconstitution inflammatory syndrome in an HIV positive patient recently started on antiretrovirals.

Table 3.12 Poor prognostic factors for all severe malnutrition (N=113) and kwashiorkor deaths (N=72)

	All patients (deaths= 13)			Oedematous malnutrition (deaths= 7)		
	Odds ratio	95% CI	p value	Odds Ratio	95% CI	p value
CLINICAL FINDINGS						
Hypothermia	**9.7**	1.6 – 59	< 0.01	**15.5**	1.9 – 125	< 0.01
Shock	**7.2**	1.9 – 26	< 0.01	**42.7**	2.9 – 638	< 0.01
Corneal ulcers	**5.7**	1.1 – 28.8	0.02	**9**	1.4 – 58.5	0.01
Pallor	**5.5**	1.1 - 27.3	0.02	**6.47***	*	0.01
LABORATORY FEATURES						
INR > 1.7	**9.8**	2.2 – 43.4	< 0.01	**24.6**	2.8 – 213.2	< 0.01
Glucose <2.5mmol/l	**9.7**	1.6 – 59.3	< 0.01	**15.5**	1.9 – 125.3	< 0.01
Haemoglobin < 6 g/dl	**5.9**	1.4 – 25.5	0.01	6.1	0.8 – 45.0	0.24
Platelets <100 ($x10^3$/µl)	**5.7**	1.1 -28.8	0.02	**23.6**	2.3 – 244.1	< 0.01
Bacteraemia	**3.4**	1.0 – 11.7	0.05	**7.3**	1.3 – 41.8	0.01
Urinary tract infection	2.7	0.8 – 9.0	0.08	2.4	0.5 – 12.1	0.26
Bicarbonate < 17mmol/l	2.3	0.6 – 7.9	0.19	2.7	0.5 – 15.6	0.24
CRP > 10mg/l	2.0	0.5 – 8.0	0.31	4.0	0.4 – 36.7	0.19
Potassium < 3 mmol/l	1.8	0.5 – 6.4	0.37	1.3	0.2 – 7.7	0.75
INTERVENTIONS						
Fresh frozen plasma	**9.7**	1.6 – 59.3	< 0.01	**23.6**	2.3 – 244	< 0.01
Blood transfusion	**7.8**	2.1 – 29.2	< 0.01	**42.8**	2.9 – 638	< 0.01
Antiretroviral treatment	3.3	0.6 – 14.0	0.09	**12.6**	0.7 - 194	0.05
TB treatment	0.2	0.01 – 1.8	0.18	0	0 – 4.0	0.59

*** OR and 95% CI could not be estimated as one cell value was zero.**
Statistically significant odds ratios have been highlighted in bold.

3.10. HIV Status

Of all HIV positive children in this study, 31 (54%) had never been diagnosed with HIV prior to this admission according to their caregivers. Only two of these children were younger than two months. The other 29 could have been diagnosed through routine testing of six week old HIV exposed infants if this were available (it is national policy to offer this).

Forty seven children had CD4 cell counts done (81%): the mean CD4% was 22%, SD 10.8. A CD4% of less than 20% was not a poor prognostic factor: 13% of those with a CD4% less than 20% died, versus 24% of those with a CD4% greater than 20% (OR 0.5, 95% CI 0.09–2.23, p= 0.3)

Twenty six HIV positive children (46%) were known to be seropositive before the current admission. Twelve of these children (46%) were on highly active antiretroviral therapy prior to hospital admission. The majority of these children (83%) were on treatment for less than two months (Figure 3.4). Of four children who were started on treatment during this admission, two (50%) subsequently demised. Two of the twelve (17%) children who were on HAART prior to this admission died; both of them had been on treatment for less than two months.

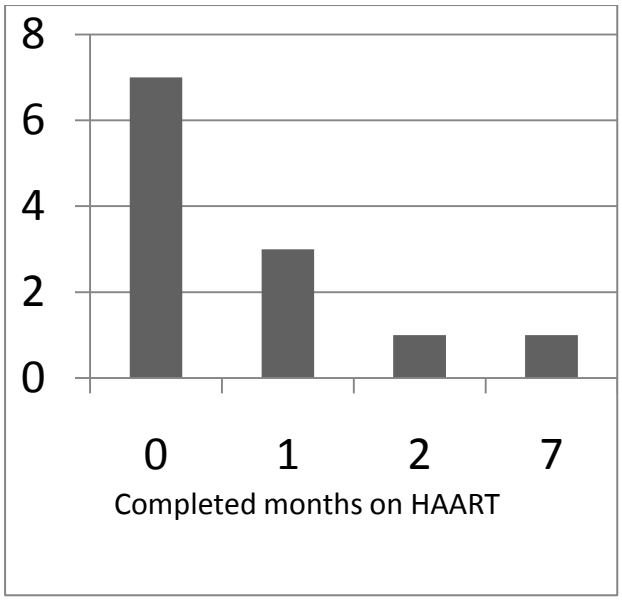

Figure 3.4 Duration of antiretroviral therapy in HIV infected children prior to admission (N= 12).

3.11. The HIV "affected" children

Among the HIV negative children whose mother's HIV status was known, just over half (19/37 [51%]) were "HIV exposed" during the intrapartum, antenatal and postpartum period. In the general population, this ratio would be expected to be significantly lower: assuming an HIV prevalence of 30% in antenatal clinics in Gauteng and a vertical transmission rate of 10%, the general population would have 3% of all children infected, 27% exposed but negative and 70% negative and not exposed. HIV affected children were thus more likely to become severely malnourished than their non HIV exposed counterparts. No difference was found in the mortality between exposed and non-exposed HIV negative children (6% and 5% respectively). None of the 18 HIV negative children whose mother's status was unknown died. The total duration of hospital stay also did not differ significantly (13.8 days vs 11.2 days, p= 0.16) (table 3.13).

Table 3.13 Differences between HIV positive, HIV exposed but negative ("HIV affected") and HIV non-exposed children (N= 95, [18 mothers' status was unknown])

	HIV positive N=58 n(%)	**HIV Affected N= 19 n(%)**	**Not HIV exposed N=18 n(%)**
Kwashiorkor	16 (28)	8 (42)	10 (56)
Marasmus	34 (59)	4 (21)	3 (17)
Bacteraemia	15 (26)	3 (16)	5 (28)
Suspected TB	17 (29)	4 (21)	4 (22)
Haemoglobin < 6 g/dl	7 (12)	1 (5)	0 (0)
Platelets < 100,000/µl	8 (14)	0 (0)	0 (0)
Case fatality rate	11 (19)	1 (5)	1 (6)

4. Discussion

4.1. Main findings:

This study confirms that a case fatality rate of less than five percent is difficult to attain in areas with a high HIV prevalence, even in well resourced settings. The only group in which this target was achieved was in HIV negative children (case fatality rate 3.6%); supporting the notion that HIV infection is largely to blame for the excess mortality. Contrary to what Schofield and Ashworth described in their literature review on case fatality rates in 1996,[25] marasmus now appears to carry a similar, if not worse, early prognosis than kwashiorkor. This effect may be explained by the higher prevalence of HIV infection in the marasmic group.

The median age of the study sample (10 months) was exceptionally young. This finding highlights the need for improved infant feeding strategies for HIV exposed infants, especially as 81% of the children whose mother's status was known were HIV exposed.

Another important finding is the contribution of HIV infection to severe malnutrition in this setting, with about half of the enrolled children being HIV positive. This sample confirmed differences between the HIV positive and negative children and the malnutrition they suffer. Similar to previous studies,[48] HIV positive children were more likely to have marasmus, while the negative group predominantly had kwashiorkor. Additionally, HIV positive children were more likely to have had previous hospital admissions; they had more hepatomegaly, splenomegaly, lymphadenopathy and respiratory distress.

The search for poor prognostic features revealed some interesting findings, despite being somewhat limited by the small number of deaths observed. Besides HIV, the presence of shock (and therefore probably intravenous fluid boluses), blood transfusions and evidence of disseminated intravascular coagulation (abnormal INR and thrombocytopaenia) were the most notable poor

prognostic factors. Additionally, some traditional risk factors (such as corneal ulcers, hypoglycaemia and hypothermia) retained prognostic significance.

As expected, bacterial infections were common and remain an important part of the disease in the HIV era. Gastroenteritis, septicaemia and urinary tract infections were common findings. Suspected tuberculosis was also prevalent in this sample, while laboratory evidence for the disease was typically scarce. It is therefore tragic that the isoniazid prophylaxis programme for young children exposed to TB contacts does not appear to be functioning well in Gauteng, with none of the children who were exposed to the disease at home being investigated or started on prophylaxis.

Deaths occurred early in the course of the disease. There was a high prevalence of septicaemia and suspected septicaemia in the group of children who died. Similarly, intravenous infusions of crystalloid fluids and blood were common, and more prudent use of these may be an area to investigate further to try and reduce mortality rates. However, the need for this intravenous therapy may also be a reflection of the seriousness of the illness in this group. Lastly, improving the Prevention of Mother to Child Transmission of HIV programme (PMTCT), and early diagnosis and treatment of HIV in infants, could greatly improve prevention and outcome of severe childhood malnutrition.

4.2. General characteristics

4.2.1. Anthropometrics

The discrepancy observed in measurement of length between the researcher and the admitting staff was alarming. A discrepancy of greater than 2.5 cm has a significant implication when translated into z-scores in children. As this was the case in 43% of patients, the prevalence of wasting and stunting may differ significantly according to how the child is measured. The difficulty in obtaining an accurate length in a busy admission ward is understandable, particularly when measuring boards may be unavailable and some of the children are critically ill. An accurate length is

critical however if weight for length z-scores of less than -3 are to be used as the definition for severe malnutrition. This has an important bearing in classifying the child at the outset and in measuring successful rehabilitation. WHO has clear guidelines how to remediate these common problems.[49]

These obstacles in measuring the length of ill children support the recommendation for more widespread use of mid-upper arm circumference (MUAC) measurements.[50] It is easier to carry out and is less likely to be susceptible to inter-observer difference. In addition, no accurate scale is required, and the measurement requires no interpretation on growth charts. The MUAC measurement has been validated in several trials and has been shown to be a good predictor of mortality in severely malnourished children, performing at least as well as a weight for length z-score of less than -3.[50, 51] These publications also describe that using a MUAC < 11.5 cm or a weight for length z-score less than -3 identifies different populations with some overlap, but MUAC is less likely to be influenced by factors such as acute dehydration or salt and fluid retention as seen in kwashiorkor. It may thus be advisable to use the MUAC < 11.5 cm in clinics and primary health care settings for diagnosing severe malnutrition, while using both measurements (MUAC and length) is advisable in hospital situations, providing staff has been trained in the performance of the correct measuring of weights, lengths and heights.

4.2.2. Patient's medical history

A sizeable proportion of children had been previously admitted to a hospital (29% of HIV negative and 62% of HIV positive children). Although no further information could be captured with regards to the number, reasons and timing of previous admissions and their nutritional status at the time of that admission, this finding highlights how the healthcare system is failing to address the nutritional needs of children with earlier forms of malnutrition. This was particularly the case in HIV positive children, where effective care had not been instituted regardless of whether or not a diagnosis of HIV had been made.

The immunisation coverage in the sample was reasonably high, especially considering the possibly difficult social circumstances the children came from. This implies a reasonable interaction with the healthcare services, and again highlights the failure of the system to identify and treat these children before they present with severe malnutrition. This failure is essentially a failure of growth monitoring and promotion (part of the Integrated Management of Childhood Illnesses programme in South Africa), which has been described in other settings.[52] Unless it is linked to adequate nutrition counselling and support, and an appropriate referral system, growth monitoring has not been shown to reduce malnutrition.[53]

In addition, the high prevalence of malnutrition is a failure of the health system to prevent the earlier forms of the disease in the first place. More emphasis needs to be placed on infant feeding strategies, particularly in the HIV setting.

4.3. Clinical presentation and laboratory features

4.3.1. Dehydration and shock

Dehydration was a very common finding (53%) despite being clinically difficult to detect in malnourished children. Similarly, a clinical diagnosis of shock was common (19%). Unfortunately, it was not possible to differentiate the type of shock; and it is thus not possible to estimate what percentage was the result of hypovolaemic, septic, or cardiogenic shock. This may have management implications, as excessive fluid resuscitation may have detrimental effects if the patient has poor myocardial contractility contributing to his/her shock, as may be the case in severely malnourished children.[54]

4.3.2. Stigmata of HIV infection

Typical but non-specific features seen in HIV infected children were frequently encountered in the HIV negative severely malnourished. Hepatomegaly, lymphadenopathy and oral candidiasis were

therefore not useful in predicting an HIV positive status. Splenomegaly was a finding that was more specific to HIV infection, but it occurred infrequently. As a conclusion, it is very difficult to predict the HIV status of a severely malnourished child from clinical findings. This has been described in previous studies.[55] With the high prevalence of HIV in severely malnourished children, this also makes the case for routinely testing all severely malnourished children for HIV in this setting.

4.3.3. Laboratory features

Serum markers suggestive of sepsis were positive in a large proportion of patients (e.g. CRP was raised in two thirds of patients). This, together with the culture-confirmed infections, confirms the high incidence of bacterial infection in severely malnourished children. This did not appear to differ between HIV infected and non-infected children, nor was it specific to the type of malnutrition. It is therefore imperative to continue the use of broad spectrum antibiotics in all children with severe malnutrition, despite the absence of strong evidence from a randomised controlled trial, for example, supporting this.

Although the mean albumin level of kwashiorkor patients was lower than the marasmic group, a significant overlap was observed (respective ranges: 9 to 38 and 19 to 40 g/dl). This supports the notion that oedema in malnutrition is not solely caused by hypoalbuminaemia.[56]

4.4. Infections

4.4.1. Bacterial infections

Bacteraemia and bacterial urinary tract infections were common in all types of severe malnutrition. The organisms implicated are similar to those described previously, with a high proportion of gram negative bacteria.[40, 44] The first line antibiotics (ampicillin and gentamicin) used in this setting remain appropriate choices.

4.4.2. Tuberculosis

The prevalence of suspected TB was high (27%). The incidence of TB cases has been rising rapidly in Gauteng,[57] and this appears to be reflected in this sample. Evidence other than suspicious X-ray findings was not found in 80% of these cases, and the validity of the diagnoses is questionable since pulmonary TB remains difficult to diagnose in children.[37] There is limited literature on the prevalence of pulmonary TB in severely malnourished children. Amadi and others reported a prevalence of 18% in a study in Zambia in 2001.[58]

It is imperative to get a better handle on the TB prevention programme, especially in children. Contact tracing and isoniazid prophylaxis to children under five years is a proven and effective strategy [59] and it appears it is not being practiced adequately in Gauteng. This needs to be addressed at a programmatic level, but physicians who are diagnosing adult or paediatric TB also need to be reminded to look for both a source of the infection and identify other contacts that require screening and/or prophylaxis.

4.5. Patient management

As mentioned in section 2.8, the management of severely malnourished children in this setting differed in several ways from the WHO recommendations, which are discussed below.

4.5.1. Feeding

Instead of the recommended F-75 and F-100 formulas suggested by the WHO,[3] the children are assessed individually by dieticians and humanised milk is prescribed. Aside from the lower levels of micronutrients in this milk, which are dealt with in the following paragraph, there are differences in the macronutrient contents of these milks. While there is a lower content of protein (0.9 vs. 1.8 to 3 g/100ml) and fat (2 vs. 4.4 to 6 g/100ml) in F-75, the carbohydrate content is higher 13.3 vs. 9 to 14 g/100ml).[3, 60] Most importantly, F-75 has a higher the caloric content than humanised milk (75 vs. 60 to 70 kcal/100ml), and this is even more important in the rehabilitation phase, when F-100 with

100kcal/100ml is used. However, during this next stage, local children are usually supplemented with additional foods.

Unfortunately, ready to use therapeutic foods which have been so successfully used in nutritional rehabilitation of malnourished children in other parts of Africa,[61] are not available to our local children.

4.5.2. Micronutrients

The micronutrient mix recommended in the WHO "ten steps" guidelines is not generally available at South African hospitals outside of a study setting.[28, 62] With the exception of potassium, these micronutrient deficiencies are not thought to contribute to in-hospital fatalities, and many recommended micronutrients were available in other forms in the hospitals included in this study. The only micronutrient deficiencies not specifically addressed were copper, selenium, iodine and magnesium. Supplementation with magnesium could be achieved by using a 50% magnesium sulphate mixture given orally or intramuscularly.[3] Despite the availability of the other required micronutrients, a large percentage of children did not receive some of the supplements, particularly multivitamins (in all groups), and zinc, vitamin A and folate in marasmic children. Even if this may not negatively affect case fatality rates, it is an issue that needs to be addressed at each hospital.

4.5.3. Measles vaccination

Measles vaccination was another frequently missed intervention. The WHO "ten steps" recommend immunising all children over six months old who do not have evidence of prior immunisation. In a setting where hospital wards are frequently crowded, these children who are immune compromised because of their malnutrition are thus placed at a significant risk. The recent outbreak of measles in the province and nationally is a reminder that measles remains a pervasive risk. Again, this deficiency needs to be specifically addressed at each hospital.

4.5.4. Highly active antiretroviral treatment (HAART)

All the children enrolled in this study qualified for HAART according to the South African national antiretroviral guidelines because severe malnutrition results in HIV positive children being classified as having WHO stage IV disease.[63] Only 12 children were on HAART prior to study admission, and two (17%) of the children died during their hospital stay (both were within the first two months of starting HAART). Of the four patients who were started on HAART during this admission, two died (50%). Although this may seem a very high mortality rate, a high mortality within 90 days of starting HAART has been previously described in Sub-Saharan African settings. This high mortality may be due to a combination of starting treatment too late in the course of HIV disease and the possible development of an immune reconstitution inflammatory syndrome (IRIS).[64]

The development of kwashiorkor has also been described as being a result of IRIS,[65] with possible reconstitution of the immune system activating the pathophysiological pathway that leads to the clinical features of kwashiorkor. This newly observed phenomenon may add further insight into the pathogenesis of kwashiorkor, even in HIV negative children.

The initiation of HAART in severely malnourished children is not a well researched field. It is unclear whether it is better to start HAART before, during or after nutritional rehabilitation and there is not enough data on the pharmacokinetics of antiretroviral drugs in malnourished children.[66] Further complicating the decision of best timing is the need to manage concurrent TB in many children. TB treatment in HIV positive children who also need HAART is tricky: both TB IRIS and possible drug interactions and toxicities need careful consideration and monitoring. In the era of HIV, the management of HIV-infected severely malnourished children needs to be better researched and incorporated into revised international guidelines.

4.5.5. Blood transfusions

Twenty five children (22%) received a blood transfusion during their hospital stay. Indications for blood transfusion according to the WHO "10 steps" guidelines are to transfuse all children with haemoglobin below 4 g/dl, and those with haemoglobins of 4 to 6 g/dl and signs of cardiac failure.[3] In this study only one child had a haemoglobin level below 4 g/dl, and 10 had a haemoglobin between 4 and 6 g/dl. However, these were only values captured on admission, and they do not necessarily reflect the pre-transfusion haemoglobin level. The indication and date of transfusions were also not captured.

The recommended packed cell transfusion volume is 4 ml/kg body weight over three hours.[3] At the study sites, the usual volumes that were transfused were 20 ml/kg, albeit somewhat slower, over four to six hours. Although volumes transfused, rate of transfusion and adverse outcomes of the transfusions were not captured, it must be noted that in previous studies blood transfusions carried poor prognostic implications for children with severe malnutrition.[32] It has not been determined whether this is linked to the actual blood transfusion or whether the need for a transfusion is an indicator of more severe disease. Further research is needed to investigate the ideal indication, volumes and rates of blood transfusions in severely malnourished children.

4.6. Outcomes

The main outcome of this study was the in-hospital case fatality rate of severe childhood malnutrition in a high HIV prevalence setting. Whereas this has been investigated elsewhere in impoverished settings,[27-29] an extensive literature review did not reveal any such studies in a resource privileged, urban academic setting. It is therefore an important finding that even in such a setting the overall case fatality remained well over 5%.

Consideration must be given to admission criteria - was this sample of children less or more sick than severely malnourished children elsewhere? The attending doctors decided whether to admit a

child or whether to follow him or her up as an outpatient. In practice, all children with oedematous malnutrition are usually admitted; but a considerable amount of marasmic patients may be treated at home. In contrast, the management of uncomplicated severely malnourished children (including kwashiorkor) elsewhere in Africa has recently been shown to be as effective when done in an outpatient setting and using ready to use food.[61, 67] This study sample may thus include less ill children compared to settings where ready to use food is available, where only "complicated" malnutrition demands admission.

Regardless of admission criteria, it remains clear that mortality rates less than 5% remain unachievable, except in HIV negative children. Clearly, HIV infection is a large contributing factor to the excess mortality seen in these children, with an odds ratio of 6.2 (95% CI 1.24–59). This once again highlights the need to research the management of this disease in HIV positive children, and to revise the WHO "10 steps" guidelines to incorporate this new research.

4.7. Prognostic factors and direct causes of death

Poor prognostic factors described in the pre-HIV era were mainly features of severe kwashiorkor, and features that could directly cause death. Severe kwashiorkor is characterised by liver dysfunction, and hence hepatomegaly, jaundice and bruising were frequently quoted as factors predictive of death. Features that may directly cause death unless treated include hypoglycaemia, hypothermia and hypokalaemia. Others, such as weeping dermatitis, are features of severe disease and may be involved in causing septicaemia. These direct causes of death were addressed in the WHO "10 steps" management guidelines, and its implementation could thus reduce fatality rates. Now that most deaths occur in marasmic and HIV positive patients, the contribution of other factors warrants study.

In this study, the search for these factors was limited by the small number of deaths observed. Nevertheless, some factors that may indicate more severe disease were once again predictive of a

fatal outcome: hypoglycaemia and corneal ulcers are examples. Several factors that may be related to septicaemia were also strongly predictive: bacteraemia, prolonged prothrombin index, thrombocytopaenia and the administration of fresh frozen plasma are examples. The latter is frequently given for intractable shock and prolonged bleeding in patients with a prolonged INR.

Pallor, shock and blood transfusions were factors that deserve a special mention. Perhaps the pallor and the shock were markers for patients that received higher volumes of intravenous fluids or blood transfusions. It is possible that the higher volume of intravenous fluids administered to children with shock predisposed these children with poorly contractile hearts to cardiac failure.[54] This is difficult to prove as the amount, date and time of infusions were not captured to compare to the time of death. Infusing large amounts of fluids and overhydration has been recognised as a cause of death in malnourished children.[25] However, these three factors are perhaps also markers of more severe disease, and an observational study such as this cannot differentiate whether the initial severe disease or the intervention was to blame for the patient's fatal outcome.

An attempt was made to assign an immediate (direct) cause of death to each child that died. Septicaemia and septic shock were the most common causes identified. This was despite the administration of intravenous antibiotics to all these children from the time of admission. To prevent similar deaths in future, the primary health care management of earlier forms of the disease and prevention of severe malnutrition must be addressed.

Several poor prognostic factors were similar to what was found in recent research by Maitland and colleagues in Kenya.[31] Hypothermia, hypoglycaemia and shock were significant common factors in both studies, and should guide the clinicians in these settings to identify patients at highest risk of death.

4.8. HIV infected children

The high prevalence of HIV in this sample and the high case fatality rate of HIV positive children identify an area where a large impact can be made on reducing child deaths from severe malnutrition. It is tragic to see that over half of the positive children in this sample, and two thirds of the positive children who died, were diagnosed with HIV for the first time during this admission. This is unacceptable in a province where there is widespread availability of prevention of mother to child transmission of HIV (PMTCT) and infant diagnosis programmes. It is possible that a proportion of patients were in fact not from Gauteng province. Place of residence was difficult to ascertain and was not captured for the purpose of this study. Another possibility is that some mothers may not be disclosing their prior knowledge that the child was HIV positive.

It is imperative that PMTCT and infant diagnosis services are strengthened in all areas to facilitate prevention of vertical transmission and early diagnosis where this prevention fails. The CHER study provides clear evidence that treating all HIV positive infants with HAART dramatically increases their chance of survival.[24] By combining improved PMTCT and early HAART for HIV positive infants strategies, government policies could have a dramatic impact on the burden of HIV on children and child mortality. A recent study by Hughes and colleagues supports this recommendation further: CD4 counts of severely malnourished HIV positive children continued to decline despite nutritional rehabilitation. By the time the children reached full nutritional recovery, over 85% required HAART because of low CD4 counts.[68]

A discussion of HIV and childhood malnutrition would not be complete without discussing the controversial topic of the feeding of HIV exposed infants. Healthcare workers and HIV positive mothers need to weigh up the risks of breastfeeding and possible transmission of the virus versus formula feeding, with the risk of malnutrition, diarrhoea and other infections, and possibly death.[69] This difficult decision is frequently complicated by biased healthcare workers, the option of receiving free formula, and the stigma associated with formula feeding in certain settings. In addition, the

issue is further complicated by the difficulty of maintaining exclusive breastfeeding in mothers who are potentially ill themselves, and by the conflicting advice on how to wean children off breast milk.[69] However; there may be light on the horizon. Evidence is accumulating that breastfeeding may be safe if the mother or infant is on antiretroviral therapy during this period,[70, 71] and it is now recommended in the new WHO infant feeding guidelines. [72]

Breastfeeding is protective against developing severe malnutrition.[22] Clearly the low rates of breastfeeding observed in this study may have contributed to the development of severe malnutrition.

4.9. HIV affected children

HIV affected (HIV exposed but negative) children are at a higher risk for malnutrition, infections, and dying.[73] This may be due to a combination of factors: less breastfeeding to avoid HIV transmission, parental illness or death and increased exposure to infections such as TB. This increased vulnerability seems to be borne out in this study: over half of the HIV negative children whose mother's status was known, were in fact HIV exposed. It may therefore be prudent to follow these children more closely than is currently the norm. More frequent visits to primary health care clinics with frequent growth monitoring and early nutritional interventions may be beneficial. Research must also be directed at the potential role of chemoprophylaxis in these children: perhaps cotrimoxazole or isoniazid prophylaxis may be warranted during infancy until they are out of the danger period.

No previous literature has reported the outcome of this group of children with severe acute malnutrition. It was encouraging to see that the HIV affected children in the study sample behaved more like the non-exposed children than the positive children. Although the numbers in these groups were too small to make statistically significant observations, case fatality rates and the types of malnutrition encountered in this group were similar to their non-exposed counterparts.

4.10. Study limitations:

The study protocol relied on the paediatric registrar on duty identifying participants and obtaining consent for study participation. Owing to their high workloads, study consent was not always a priority for registrars when caring for critically ill children and a number of eligible cases were missed. The researcher tried to obtain consent for including these "missed" children into the study at a later stage but the child's caregiver was sometimes not available, and the child could then not be included into the study. Recognising that this might have significantly limited study enrolment, the researcher subsequently left consent forms in the patients' files to be filled out by the attending doctor once the caregiver arrived for a visit. The researcher has no way of knowing how many cases may have been missed, but in his opinion these strategies limited the number of such children, and this did not affect the validity of the observations significantly.

A comparison of patients identified using the WHO criteria and the Wellcome criteria could not be made because few patients were identified and enrolled for the study if they did not meet Wellcome criteria. This is probably because the WHO criteria are little known and seldom used in South African hospitals. Although this difficulty in enrolling patients who did not fulfil Wellcome criteria limits the study's ability to assess the differences between the two definitions, this was not the study's main objective.

The information needed for the history section of the questionnaire was taken from the child's bed-letter when the caregiver was not available, so this information could not be verified and was sometimes incomplete. This limited the amount of analysis that could be done on the history section of the questionnaire. But this was once again not one of the study's main objectives.

Owing to limited time and resources, only initial blood samples and their results were captured, while ward management decisions to start second line antibiotics, blood transfusions, etc. were captured over the entire stay. Of particular concern was the lack of documentation of tuberculin skin

test results. The result of this test was often not noted in the file or laboratory result sheet, and it was thus difficult to follow up its results. Although it may be reasonably assumed that a positive skin test result would have been noted in the file, no test was assumed to be negative if not specifically noted in the file or physically seen by the researcher. However, capturing this additional information would not have altered any of the results discussed above.

Owing to the fact that the researcher could not physically visit every hospital every day, many files were not reviewed after the child's discharge or transfer. However, the visits were timed so that no child would be missed for more than four consecutive days, hence limiting the extent of potential missed recording of interventions and events prior to discharge. All charts of children who died were reviewed by the researcher after the child's demise.

Ideally the study question required a long term follow-up study to document how many children reach the recommended discharge criteria of 90% of expected weight for height,[3] particularly as high incidences of mortality beyond the initial stabilisation phase have been described.[66] However this was not possible in the short period of time available for the research report.

Finally, the sample size calculation as reported in section suggested a sample size of 318 patients, which was difficult to achieve in a short period of data collection. The researcher was fortunate that a more limited sample size proved adequate. Given the observed mortality rates of 3.9% and 19%, using a significance level $\alpha = 0.05$ and the observed case: control ratio of 1:1, the power of the study was calculated to be 0.92.

4.11. Areas for future research:

- The management of HIV in the face of severe malnutrition: the indications and timing of TB treatment, HAART and nutritional rehabilitation need further research to help generate appropriate guidelines.
- The management of shock and severe anaemia in severely malnourished children: indications and recommendations for intravenous therapies need to be devised to address this remaining cause of mortality.
- The safety of breastfeeding HIV exposed infants while mother or baby is on HAART needs more evidence: how low are the transmission rates and is there any toxicity from the baby's exposure to antiretroviral drugs excreted in breast milk?
- HIV negative but exposed children form a large group and they are vulnerable to excessive morbidity and mortality: their need for possible closer follow-up, socio-economic and pharmacological interventions is an under-researched area.

5. Conclusion

HIV was directly or indirectly responsible for most of the severe malnutrition seen in children admitted to the paediatric wards at the Johannesburg group of academic hospitals. The infection has changed the pathophysiology and mortality rates of malnutrition in Johannesburg. When evaluating the performance of an institution's management of malnutrition, case fatality rates should be separated into what is achieved in HIV negative children, and positive children. While the WHO guidelines address how to manage the traditional nutrition-related malnutrition seen in the pre-HIV era, there is a dire need for new guidelines to assist in lowering the mortality rate in HIV positive malnourished children.

Despite getting care in a relatively resource privileged setting, some basic steps in the management of malnutrition were not being practised consistently. There is a need for standardised protocols for all doctors in these hospitals to manage malnutrition. This may include the option of using the WHO definition for severe malnutrition and using mid-upper arm circumference measurements to broaden the net and to include more patients into the definition. Protocols will help to ensure that all those who qualify receive micronutrient supplements and measles vaccine, and to reinforce the use of broad spectrum antibiotics for all categories of children with severe malnutrition.

Accurate measurement of length proved difficult in the admission ward setting. This can be extrapolated to mean that children visiting primary care clinics are probably also not measured accurately. It may thus be time to advocate for the more widespread use of mid-upper arm circumference measurements, which are easy to perform and to interpret.[12] Its use may increase children's opportunity to access the nutritional support they need.

Tuberculosis is a common infection in malnourished children. The diagnosis of pulmonary tuberculosis disease remains difficult in children, and emphasis must be placed on an effective contact tracing, screening and prophylaxis programme.

Ultimately, intervention must be aimed at the prevention of malnutrition, and it seems there may be much that could be done to address this. Firstly, the growth monitoring and promotion programme needs strengthening through improved nutrition counselling, food supplementation and better referral systems. Secondly, breastfeeding must be promoted in all HIV negative mothers, and possibly also all positive mothers on antiretroviral treatment. Prevention of mother to child transmission of HIV programmes need expansion to ensure that all pregnant women have an opportunity to test for HIV and get appropriate antiretroviral therapy to diminish vertical transmission rates. If an infant is infected, early diagnosis and early antiretroviral treatment is the key to avoid a high risk of morbidity and mortality. Lastly, HIV affected children require more routine attention. This may include closer follow-up and monitoring, access to social services and financial aid where parents are ill or dead and possibly chemoprophylaxis to prevent common infections.

6. Recommendations

- Monitoring of programme performance of in-patient management of severe malnutrition should address the case fatality rates of HIV positive and negative children separately.
- Hospital protocols for the management of severe malnutrition are needed in the study setting.
- There should be more widespread use of mid-upper arm circumference measurements to identify severely malnourished children.
- The provincial tuberculosis contact tracing, screening and prophylaxis programme needs to be drastically improved.
- Programmes aimed at preventing malnutrition such as the growth monitoring and promotion and PMTCT programmes require attention.
- HIV affected children should be followed up as part of the prevention of mother to child transmission programme. They are a vulnerable group and may need more medical, social and financial assistance. This is a research priority.
- Prevention of mother to child transmission programmes need to be expanded to ensure a lower transmission rate. The results of studies examining the safety and efficacy of breastfeeding while antiretroviral treatment is provided to the infant or mother are awaited with interest. The recently published feeding guidelines for HIV exposed infants from the World Health Organisation support this.[72]
- Infants infected with HIV should be diagnosed early and started on antiretroviral treatment immediately to help prevent further morbidity and mortality, including malnutrition.

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APPENDIX A - Data collection form

Section 1: History

	Personal details					
Snum	**Study number**					
Dob	**Date of birth**					
Sex	**Sex**					
Pob	**Place of birth**	1= Hospital	2= Clinic	3= Home	4= Other	5= Unknown
Doa	**Date of arrival**					

	Anthropometrics					
mr	**Measurements redone?**	☐ Yes	☐ No, taken from file		Z-scores	
Wt	**Weight** (kg)					
Lt	**Length/Height** (cm)					
HC	**Head circumference** (cm)					
MUAC	**Mid upper arm circumference**					
Oed	**Oedema**	☐ Yes	☐ No	**Wt for Lt Z score**		
Wast	**Severe visible wasting**	☐ Yes	☐ No			
WHO	**WHO severe malnut**	☐ Yes	☐ No			
Well	**Wellcome class**	1= Normal	2= Under	3= Maras	4= Kwashi	5= Mar-Kw

	HIV status – Child				
HIVe	**HIV exposed?**	1= Yes	2= No	3= Unknown	
HIVp	**HIV PCR**	1= Positive	2= Negative	3= Early Neg	4= Unknown
PMC	**PMTCT given?**	1= No	2= NVP	3= NVP + AZT	4= N/A	5= Unknown
ARV	**On HAART**	☐ Yes	☐ No			
ARVd	**Time on HAART**	Months				
CD4	**CD4% prior to admission**		VL	**Viral load prior to admission**		

	HIV status – Mom						
mARV	**Mom on HAART?**	1= Yes	2= No	3= Unknown	4= N/A	5= Mom not around	
mARVd	**Time on HAART**	Months					
mPMC	**Received PMTCT?**	1= No	2= NVP	3= AZT + NVP < 4/52	4= AZT + NVP > 4/52	5= N/A	6= Unknown
mCD4	**Last CD4**		mVL	**Viral load**			
mWHO	**WHO status**						

	Main complaint								
Dia	**Diarrhoea (Y/N)**	☐ Yes	☐ No	dDia	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
Vom	**Vomiting (Y/N)**	☐ Yes	☐ No	dVom	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
Cou	**Cough (Y/N)**	☐ Yes	☐ No	dCou	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
Fev	**Fever (Y/N)**	☐ Yes	☐ No	dFev	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
oSx1	**Other symptom**			doSx1	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
oSx2	**Other symptom**			doSx2	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
oSx3	**Other symptom**			doSx2	**Duration**	1=<1wk	2=1-2w	3= >2w	4= Unkn
TBc	**Close TB contact?**	1= Yes	2= No	3= Unknown	TBp	**TB prophylaxis**	1= Yes	2= No	3= Unknown
Coad	**Adult with chronic cough in household?**				☐ Yes	☐ No			

Previous admissions		
pAdm	**Previously admitted?**	☐ Yes ☐ No

Medications and muthi in last week							
Med	**Recorded?**	☐ Yes ☐ No					
Med1-5	1= ARV's	2= TB Rx	3= TB proph	4= Bactrim	5= other a'bic	6= MVT	7= Fe
Medo1-4	**Other meds**						
Muthi1-4	**Muthi + other**						

Road to Health card and immunisations					
RTHC	**RTHC seen**	☐ Yes ☐ No			
Imm	**Immunisations**	1= Up to date	2= Incomplete	3= Never immunised	4= Unknown

Milestones		
Mile	**Milestones**	☐ Appropriate ☐ Delayed

Feeding						
BF	**Breastfeeding?**	1= Yes, current	2= Yes, previously	3= Never	4= Unknown	
BFs	**If BF stopped, at what age?**	Months				
FF	**Formula feeding?**	1= Yes, current	2= Yes, previously	3= Never	4= Unknown	
FFs	**If stopped, at what age?**	Months				
FP	**Formula preparation**	1= Adequate	2= Inadequate	3= Unknown		
FPp	**Problems with formula prep**	1= Too dilute	2= Too strong	3= Not hygienic	4= Inadequate quantity	5= Other:
Sol	**Solids?**	1= Yes	2= No	3= Unknown		
Sola	**Age of first solids**	Months				

Social history									
Hous	**Housing**	1= Brick house	2= Flat	3= Shack	4= Other	5= Unknown			
RW	**Running water**	1= Yes inside/ in yard	2= Yes on street	3= No	4= Unknown				
FT	**Flushing toilet**	1= Yes	2= No	3= Unknown					
Elec	**Electricity**	1= Yes	2= No	3= Unknown					
Mcg	**Main caregiver**	1= Mother	2= Father	3= Grandparent	4= Aunt	5= Other			
mal	**Mother alive**	1= Yes	2= No	3= Unknown					
fal	**Father alive**	1= Yes	2= No	3= Unknown					
Memp	**Mother employed**	1= Yes	2= No	3= Unknown	4= Mother AWOL				
Femp	**Father employed**	1= Yes	2= No	3= Unknown	4= Father AWOL				
CSG	**Child support grant**	1= Yes	2= No	3= Unknown					
Oinc	**Other income**	1= Other grants	2= Grandparents support	3= Piecework	4= Other	5= Unknown			
Bord	**Birth order**								
Sibs	**Number of siblings**		Sibd	**Siblings who died (No)**					

Section 2: Examination

Vitals on admission					
HR	**Heart rate**	Bpm	RR	**Resp rate**	Bpm
Temp	**Temperature**	˚C			

General – please tick								
Pale	**Pallor**		Deh	**Dehydration**		RDS	**Resp distress**	
Jau	**Jaundice**		Shk	**Shock**		EDC	**Ear discharge**	
hog	**Hypoglycaemia**					NR	**Napkin rash**	
Wder	**Weeping dermatitis**		Ocan	**Oral candida**		Pet	**Petechiae**	
ASto	**Angular stomatitis**		LAD	**Lymphadenopathy**		Bru	**Bruising**	
BdF	**Bulldog facies**		HaC	**Hair changes**		cul	**Corneal ulcers**	
HoT	**Hypothermia**		Hepa	**Hepatomegaly**		Splen	**Splenomegaly**	

Systems examination					
HMs	**Hepatomegaly size**	Cm below ribs	Spls	**Spleen size**	Cm below ribs
OEo	**Other findings**				

Section 3: Laboratory values on admisssion

FBC	**WCC**		**Hb**		**MCV**		**Plts**	
U&E	Na		K		CO2		Urea	
LFT	SBR		TP		Alb		CRP	
Other	Glucose		INR		CD4 (%)		CD4(abs)	
	VL		CCa		PO4		Mg	
Urine	UTI	☐ Yes ☐ No	**Culture**		Ucult			
Blood culture	bcpos	☐ Yes ☐ No	**Organisms**		Org1-2			
Tuberculosis	PPD	1= Pos 2= Neg 3= Not done			AFB	1= Pos	2= Neg	3= Not done
CSF	Men	☐ Yes ☐ No	**Organism**		morg			
Other	loth							

Section4: Management

Rx given during hospital stay							
	Antibiotics – Tick all	1= Ampi	2= Genta	3= Tazocin	4= Amik	5= Mero	6= Vanco
		7= Ceph	8= Clox	9= Bactrim	10= TB Rx	11= Other:	
hBTF	**Packed cell transfusion?**	☐ Yes ☐ No					
hARV	**HAART**	☐ Yes ☐ No					
hffp	**Fresh frozen plasma**	☐ Yes ☐ No					
hMaln 1-5	**Malnut regime etc: Tick all**	1= Mist KCl	2= Zinc	3= Vit A	4= Vit K		
		5= MVT	6= Folate	7= Iron	8= Measles vaccine		
hOth1-3							

Section 5: Outcome

Outc	**Outcome**	**1= Discharged home**	**2= Died**	**3= Transferred out**	**4= RHT**
dOut	**Date of outcome**		dWt	**Weight**	
dDx1	**Other diagnoses**		dHt	**Height**	
dDx2	**Other diagnoses**		dOed	**Oedema**	☐ Yes ☐ No
dDx3	**Other diagnoses**				

Section 6: Death & CHIP forms

CoD1	**Causes of death**	
CoD2	**Causes of death**	
CoD3	**Causes of death**	
CHIP	**CHIP form filled**	☐ Yes ☐ No
Avfac 1-5	**Avoidable factors (list)**	

Section 7: Additional comments

APPENDIX B – Ethical approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 De Maayer

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M080809**
PROJECT	The Impact of HIV on Severe Childhood Malnutrition
INVESTIGATORS	Dr T De Maayer
DEPARTMENT	Department of Paediatrics
DATE CONSIDERED	08.08.29
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 08.09.08 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Prof H Saloojee

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX C – Gauteng Department of Health approval

DEPARTMENT OF HEALTH

DIRECTORATE: POLICY, PLANNING & RESEARCH
Enquiries: Dr Likibi
Tel :(011) 3553144/3477
Fax: 0865382979
Email: Mupata.Likibi@gauteng.gov.za

Date: 06 August 2008

Attention: Dr T De Maayer
Fax: 0865534545

Notice of Research Protocol Review

This is to inform the researcher (Tim De Maayer) the protocol titled: '**SEVERE MALNUTRITION IN THE HIV/AIDS ERA: Examining case fatality rates, prognostic factors and classification**' is in the process of being reviewed by the Research and Epidemiology sub-directorate, Policy, Planning and Research Directorate in the Central Office.

For the review process to be finalised and unconditional approval granted, an Ethical Clearance Certificate is required from the researcher.

This conditional authorization is limited/subject to:

- Ethical clearance certificate submitted to the above office

Kindly note that it is also compulsory to request permission from the facility managers.

Reviewer:

Dr Y Kolisa
Research and Epidemiology Technical Support

The Evaluator:

Dr ML Likibi
Medical Specialist
Date: 6/08/2008