

**Prognostic factors in children with severe acute
malnutrition at a tertiary hospital in Cape Town, South
Africa**

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DECLARATION:

I, the undersigned, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Signature:

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Date: 24 November 2014

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ABSTRACT:

Severe acute malnutrition (SAM) remains a common problem worldwide and causes many childhood deaths. The World Health Organisation (WHO) aims for a case-fatality rate of <5% and has an established protocol to optimally manage patients.

AIMS AND METHODS: We aimed to identify prognostic factors affecting the outcome of children under the age of 5 years admitted with severe acute malnutrition with oedema. This was a retrospective descriptive study over 2 years at a tertiary hospital in Cape Town, South Africa, documenting demographic details, co-morbidity including HIV exposure or infection, referral pattern, laboratory results, complications and clinical outcome.

RESULTS: There were 59 patients with a median age of 12 months of whom 33 (56%) were male. Thirty-two children (54%) already had documented growth faltering and 9 of these 32 children (28.1%) died. There were 24 patients (40.6%) transferred from other hospitals, and they did significantly worse than children referred from community clinics (mortality rate 58.3% vs. 5.7%) ($p<0.01$). Fourteen children (23.7%) were HIV positive with a mortality rate of 42.8%. The overall mortality was 28.9%, with 81% of deaths occurring within the first 72 hours. Liver impairment ($p<0.05$), very low serum phosphate ($p<0.01$), and positive blood cultures ($p<0.02$) were all significantly associated with an increased risk of dying.

CONCLUSION: Our mortality rate for SAM is high. Children with SAM need to be carefully assessed and managed, particularly during the first 72 hours, when mortality is highest, with additional vigilance in those who have poor prognostic factors. Growth faltering should be identified early and appropriately acted upon.

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INTRODUCTION

Severe acute malnutrition (SAM) represents a medical emergency and its management should be regarded as a public health priority. It constitutes 11% of the total global burden of disease, and is an underlying factor in many preventable childhood deaths each year.¹ Many cases are complicated by coexisting infective illnesses which contribute to both the morbidity and mortality of this serious condition. Furthermore, the HIV–epidemic has resulted in the number of severely malnourished children in sub-Saharan Africa increasing, as well as causing a rise in case-fatality rates.²

The WHO has developed a set of guidelines aimed at the management of SAM.³ This guideline covers many important aspects of well-recognized prognostic features (such as hypoglycaemia, sepsis, etc.) and has recently expanded to address the challenges of caring for the HIV-infected malnourished child. Recommendations on HIV testing, initiation of antiretroviral therapy (ART) as well as therapeutic feeding strategies are now included in the WHO guideline.⁴

Through the implementation of their guideline, the WHO hopes to achieve a case-fatality rate of less than 5% amongst children younger than 5 years affected by SAM. Unfortunately in sub-Saharan Africa the mortality rate for SAM has remained higher than the WHO target. Whether this is attributable to poor case management or the clinical severity of patients is not entirely clear in the literature. However, a Kenyan-based study showed that the combination of proper WHO protocol-driven management coupled with adequately trained medical staff failed to reduce the SAM mortality rates sufficiently. While the WHO cautions against the use of intravenous fluids, their study shows evidence that hypovolaemic shock may have contributed

significantly to poor patient outcome.⁵ This suggests that there may be additional prognostic factors and management strategies not considered in the WHO guidelines which are relevant to our setting.

BACKGROUND

Globally, it is estimated that one in four children are malnourished. In 2011, approximately 101 million children worldwide under the age of 5 years were underweight (weight-for-age <-2 Z-score), 165 million stunted (height-for-age <-2 Z-score), and 52 million wasted (weight-for-height <-2 Z-score). Wasted children are at great risk of progressing to severe acute malnutrition and death.⁶ Locally, there appears to have been an improvement in the nutritional status of young children in comparison with data from 1999.⁷ However, a recent survey of children between the confirmed that malnutrition still remains a serious problem in South Africa. There is a reported rate of 12.9% for stunting and 2.9% for wasting in children between the ages of 0 and 14 years.⁸

SAM can be defined as a measurement of <-3 Z-score below the World Health Organization standards for weight, length or weight-for-height and /or symmetrical oedema involving at least the feet, in children under 5 years. It is a potentially life-threatening condition and requires urgent treatment.⁹

Malnutrition is responsible, either directly or indirectly, for more than 50% of the 10-11 million annual preventable deaths in children under 5 years.¹⁰ Risk factors for malnutrition are poverty, poor feeding practices, large family size and parenteral illiteracy.⁷ The risk of mortality is directly related to the severity of malnutrition. In sub-Saharan Africa the case fatality rate for SAM has been reported to be greater than 20%, and in some other African countries it is $>50\%$.^{11,12} Deaths are attributed to nutritional deprivation as well as complications such as electrolyte imbalances, micronutrient deficiencies and sepsis. Many cases of SAM are further

complicated by concurrent infective illnesses, particularly acute respiratory infection, diarrhoea, gram-negative septicaemia, and HIV. In HIV-infected children, this may be due to a number of factors including the increased risk of infections, the negative effects of HIV infection on nutrition, Immune Reconstitution Inflammatory Syndrome (IRIS) and drug side-effects.²

Malnutrition has been shown to have long-term implications such as growth retardation, behavioural problems, and poor cognitive performance. The extent of these complications is dependent on the severity of malnutrition, the duration of the insult, and the stage of childhood development.¹³

AIMS

The primary aim of this study was to describe the clinical features and outcomes of children admitted with severe acute malnutrition with oedema, comparing those who died with survivors, in order to identify prognostic factors and compare these with those previously described in the literature. Our secondary aim was to identify aspects of management in the hospital setting that could be modified to improve the outcome of severely malnourished children with oedema

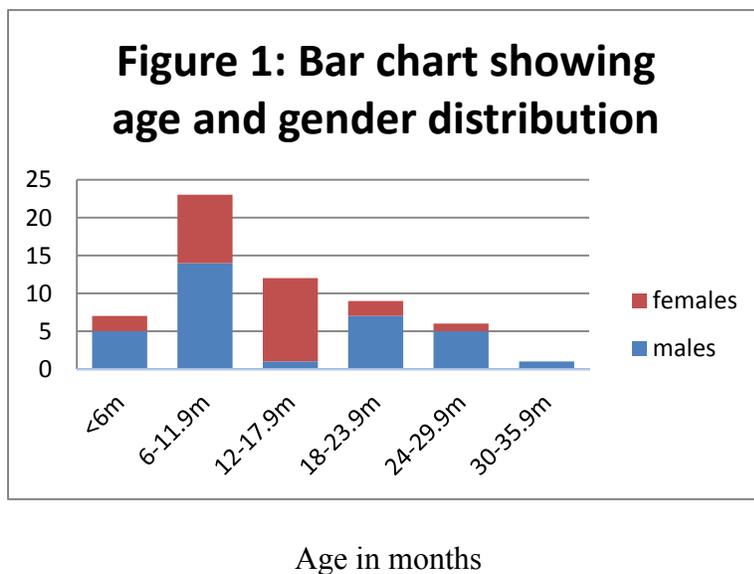
METHODS

This was a retrospective descriptive study. All children under the age of 5 years with severe acute malnutrition with oedema admitted to the Paediatric Gastroenterology Unit of Tygerberg Children's Hospital (TCH) over a 2 year period between 01 January 2008 and 31 December 2009 were included. These children had either been admitted directly to TCH from a primary health clinic within the drainage area, or from a level-one / level-two hospital if the response to initial management was poor or the clinical severity warranted specialist care. The patients were

identified through the ward admission / discharge database and their folders and laboratory data manually analysed. The following parameters were recorded: demographic details, co-morbidity including HIV exposure or infection, referral pattern, clinical management within the first 72 hours of admission, laboratory results, complications encountered during hospital stay, clinical outcome, and if applicable, time to death. Patients were excluded from the study if the initial diagnosis of SAM was later found to be incorrect or if clinical records were no longer available. Upon admission to our hospital patients were managed according to WHO guidelines. All laboratory tests were performed at the National Health Laboratory Service (NHLS) at Tygerberg Hospital with standard laboratory techniques. A child was classified HIV-exposed if the mother was tested HIV-positive during pregnancy, and HIV-infected if there was a positive HIV DNA PCR in children younger than 18 months, or by 2 positive HIV ELISA tests if 18 months or older. Information copied into patient notes from the Road to Health Chart (patient held health record) was also captured and analysed. Data was originally captured on data acquisition forms, and later transferred to an Excel® spread sheet and then to an Access ® Database. Patient confidentiality was maintained by assigning each study candidate a study number, all identifiable data was removed from the data capture tools. The study was approved by the Human Research Ethics Committee of the Faculty of Health Sciences, Stellenbosch University, and the hospital CEO provided consent for access to medical records. Statistical analysis was performed using Statistica® version 10 (StatSoft). Results have been summarised as either means with standard deviations or as medians with interquartile ranges. Categorical data were compared using the Chi Square test and medians with the Wilcoxon Rank Sum test. A p value of less than 0.05 is considered to be statistically significant.

RESULTS

Sixty-eight patients were identified for the study of which 9 were excluded. A total of 59 patients with a median age of 12 months (range 1-37 months) were included, of whom 33 were male (56%). Figure 1 shows the age and sex distribution. The average percentage of expected weight 77.03%. Thirty children (50.8%) had a weight – for– age Z–score (WAZ) of >-2 . Mean WAZ was -2.15 . Patient length was not routinely captured by the attending clinician and was therefore excluded from the analysis. Neither age nor weight distribution was affected by HIV status.



The patient-held Road to Health Chart had been inspected in 44 cases (74.5%). Fourteen children (23.7%) were behind on standard immunisations, of which 5 died (35.7%). Thirty-two children (54%) had documented growth faltering, of which 7 (21.8%) had already been referred for nutritional assessment and supplementation in the community. Of these 32 children 9 died (28.1%). Information regarding serial growth measurement and failure to thrive was not

available for 27 (45.7%) of the 59 children.

Thirty-five children (59.3%) had been referred to the hospital from primary health care clinics and 24 (40.6%) from another hospital. Table 1 shows the mortality rates according to referral facility. The mortality rate was significantly higher for those who had been transferred from other institutions compared to those who had been admitted directly ($p < 0.01$). The average length of hospitalisation at our facility was 20 days (range 0.3-112 days).

Referral facility	Survivors	Non-survivors	Mortality Rate
Community clinic n=35	33	2	5.70%
Hospital (level 1 or 2) n=24	10	14	58.3%

Table 1: Mortality rates per referral facility

HIV infection

Fourteen patients (23.7%) were HIV –infected, 11(18.6%) were HIV-exposed but PCR negative, and 4 (6%) were HIV-exposed but had not had a PCR performed yet. Seventeen children (28.8%) were HIV unexposed and tested negative, 10 (16.9%) had no record of exposure history but tested negative, and 3 patients (5%) had no obtainable record of HIV status or exposure. Table 2 shows outcome of children according to HIV status. Six of the 14 HIV infected children died (42.8% ; $p=0.31$). One HIV-exposed-uninfected child died. Five of the HIV infected

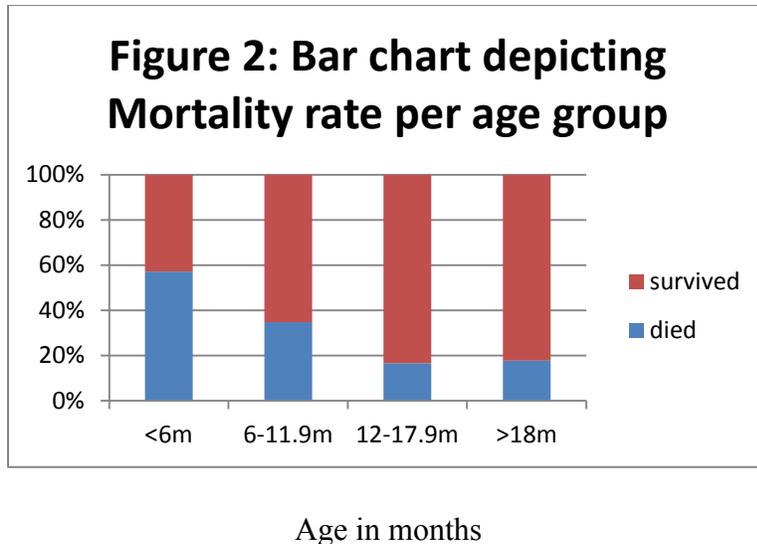
patients (35%) were already receiving Anti-retroviral therapy (ART), of which 2 died (40%). The duration of treatment with ART's for these 2 children was 5 months and 16 months respectively.

HIV status	Survivors	Non-Survivors	Mortality rate
HIV infected n=14	8	6	42.8%
HIV uninfected n=38(11 exposed negative, 27 neg)	29	9	23.7%
HIV status unknown n=7 (4 exposed, 3 not tested)	5	2	28.5%

Table 2: HIV status compared with clinical outcome

Mortality and Risk factors

There was an overall mortality rate of 28.9% (17/59), with 81% of children dying within the first 72 hours of admission. Children under the age of 1 year tended to have a worse clinical outcome, with mortality rates of 57.1% for the 0 – 6 month age group, and 34.7% for the 6 - 12 month group. For those over one year of age, the mortality rate was 17.8% (5/28).



Temperature and Blood glucose

Table 3 shows the blood glucose at time of admission to the ward. Twelve children (20.3%) had no record of blood glucose at time of presentation to our hospital. One of these twelve children subsequently died (8%). The lowest recorded blood glucose measurement at time of admission was 3.5mmol/l for survivors and 0.6mmol/l for non-survivors. Neither admission temperature nor blood glucose ($p=0.2$) were identified as being significantly associated with mortality. The mean temperature on admission was 36.5 and 36.6 degrees Celsius for survivors and non-survivors respectively.

Figures 4 and 5 demonstrate that low temperature within the first 72 hours of admission was a stronger predictor of death than admission temperature. The lowest mean temperature recorded within the first 72hrs of presentation was 35.8 degrees Celsius for survivors and 35.2 degrees Celsius for non-survivors ($p=0.004$).

Status	Mean glucose at presentation	Standard Deviation
Survivors n=31	7.52	4.956
Non-survivors n=16	9.91	7.647
<i>All groups n=47</i>	<i>8.34</i>	<i>6.033</i>

Table 3: Mean glucose at time of presentation (p=0.2)

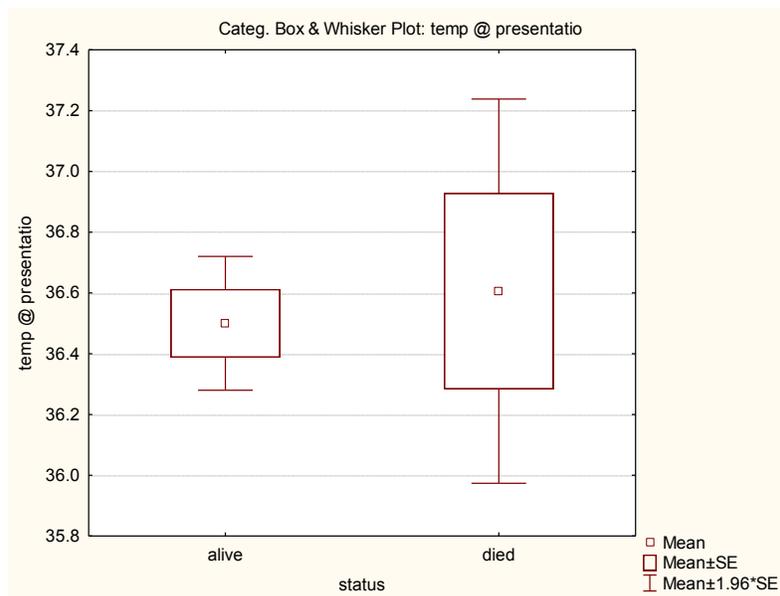


Figure 3: Box & Whisker plot showing temperature at time of presentation

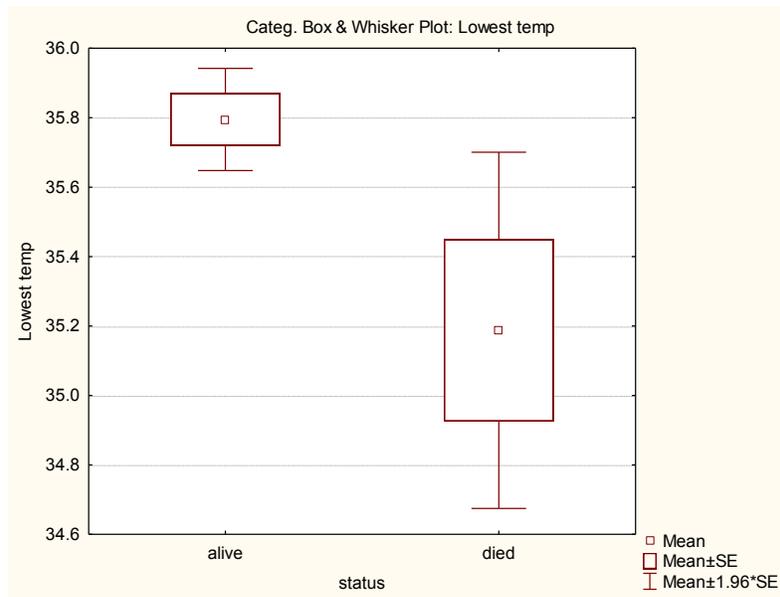


Figure 4: Box & Whisker Plot showing lowest temperature within first 72 hours of presentation

Laboratory findings

Table 4 shows the mean laboratory values for liver biochemistry and phosphate levels for the children who had these values measured. Bloods were taken at time of admission to our hospital. Children who died had significantly higher ALT (120 vs 60) and total bilirubin (71 $\mu\text{mol/l}$ vs 34 $\mu\text{mol/l}$) levels with mean values being double that of the survivors group. In addition to this they also displayed significantly more prolonged INR and lower minimum phosphate levels than their surviving counterparts.

Variable(mean)	Survivors	Non-survivors	Significance
Maximum bilirubin $\mu\text{mol/l}$ (n=37)	34	71	p=0.008
Maximum ALT U/l (n=37)	60	120	p=0.04
INR (n=32)	2.1	5.9	p<0.001
Minimum phosphate mmol/l (n=59)	0.86	0.6	p<0.01

Table 4: Various laboratory findings and their clinical outcomes

Fifty-one blood cultures were done of which 9 were positive (17.6%). Table 5 shows the outcome of children with positive blood cultures, and the organism cultured. Six of the 9 children with positive blood cultures died (66.6% ; $p=0.02$). Seven of the nine positive cultures were gram negative organisms. Ten patients with proven negative cultures died (23.8%).

Status	Organism
Alive	Escherichiae coli
Alive	Streptococcus pneumonia
Alive	Klebsiella pneumonia
Died	ESBL Klebsiella pneumonia
Died	Enterobacter cloacae
Died	Gram negative bacilli, unspecified
Died	Escherichiae coli
Died	Gram positive bacilli, unspecified
Died	ESBL Klebsiella pneumonia

Table 5: Analysis of organisms cultured from blood and their clinical outcomes

*ESBL = Extended-spectrum beta-lactamase producing organism

Co-morbidity

Table 6 shows a summary of children with specific presentations or co-morbid conditions. Forty-two children (71%) had associated diarrhoea and 31(53%) chest infections at the time of presentation, but these were not identified as being associated with a significant increase in mortality (diarrhoea $p=0.1$; pneumonia $p=0.37$). Three children presented with a history of convulsions. Oedema was a volunteered presenting symptom in only 11 cases (19%).

Presenting symptom/ comorbid condition	Total	Deaths
Diarrhoea	42	15 (35.7%)
Chest infection	31	11 (35.4%)
Fever	21	6 (28.5%)
Loss of appetite	15	4 (26.6%)
Loss of weight	11	0 (0%)
Skin Rash	11	2 (18.1%)
Oedema	9	1 (11.1%)
Lethargy	4	1 (25%)
Convulsions	3	2 (66.6%)
Jaundice	1	0 (0%)
Mouth sores	1	0 (0%)
Pericardial effusion	1	0 (0%)

Table 6: Summary of presenting complaints and the number of children with each complaint

who died

DISCUSSION

The overall mortality of this study was 29%, which is much higher than that recommended by the WHO. However it is a tertiary referral centre for complex cases. The majority of deaths occurred within the first 72 hours of admission to our health-care facility, with those under the age of 1 year having an increased risk of dying. Deaths were likely due to both severity of illness as well as delayed presentation. There was a ten-fold difference in mortality between children referred to us directly from a primary health care (PHC) clinic and those transferred from a level 1 / 2 hospital for further care. No direct comparison pertaining to prognostic factors was made between these two groups of patients. However, many of those children in the latter category were in a pre-morbid state on arrival, and died shortly after admission to our facility. None of these children had been transferred on the same day that they were admitted to their initial hospital. Although the aim of this study was not to determine the length of hospitalization prior to transfer, it is clear to the authors that under-recognition of disease severity and/or delay in transfer to a tertiary centre contributed significantly to the poor outcome of these patients. Due to study design limitations we did not have access to other hospital records so are unable to make any deductions regarding the appropriateness of care received before transfer. However, we do feel that in addition to basic management, a malnutrition management guideline should also include “red flag” signs which alert the clinician to children requiring urgent / semi-urgent transfer to a higher level of care.

More than half of our patients’ Road to Health booklets depicted growth faltering. Despite this,

only 7 of 32 children had been referred for nutritional support in the community. While it is encouraging that children's growth parameters are being measured and plotted on growth charts, the correct interpretation and management of these parameters is crucial. Primary health care clinics are the access point to the healthcare system, and primary care workers should be competent in identifying children at risk, and intervene timeously with referrals for nutritional support and other appropriate forms of social welfare. Our greatest number of patients were in the weaning phase i.e. 6 – 12 months of age, and we as healthcare providers should be particularly vigilant in monitoring the growth and development of this extremely vulnerable group of children.

HIV infection

The HIV-epidemic in Sub-Saharan Africa has resulted in an increase in the number of severely malnourished children. In a study of more than 4500 children with all categories of SAM, 29% were found to be infected with HIV, with a three-fold increase in mortality compared to their HIV-uninfected counterparts.¹¹ Several other studies have shown similar results.^{15,16} This may be due to a number of factors including the increased risk of comorbid infections, the negative effects of HIV infection on nutrition, the development of an immune reconstitution inflammatory syndrome (IRIS), and the effects of various anti-retroviral drugs.² Our rate of HIV infection has shown to be similar. While small sample size may have rendered the statistical interpretation of the mortality rate in this particular subset of patients as “not significant”, we do believe it to be of great clinical importance, and thus the extremely high mortality rate of 43% in the HIV - infected group must be appreciated.

It is of concern that 30% of our study population known to be HIV-exposed had not yet had their

definitive HIV status established prior to admission. All these children were older than 6 months. The current national policy dictates HIV DNA PCR testing at primary care level for all HIV-exposed infants at 6 weeks of age. This suggests a breakdown in the Prevention of Mother-to-Child Transmission (PMTCT) programme. Any child presenting with SAM should have their HIV status checked urgently as this impacts on short- and long- term management.

There is limited data available on long-term outcomes of children with severe malnutrition complicated by HIV. Thus far, studies done on the timing of ART initiation in severely malnourished children have shown conflicting results, with some suggesting that earlier initiation leads to improved outcomes,¹ while an Africa – based study reports clinical deterioration within 12 weeks of ART initiation.¹⁷ Reasons for possible deterioration include the unmasking of pre-existing infections (IRIS phenomenon), and anti – retroviral drug toxicity.¹⁷ However, despite poor evidence, the WHO strongly recommends that severely malnourished children qualifying for lifelong antiretroviral treatment should be initiated onto ART once metabolic complications have stabilized and sepsis resolved, and that they should then be closely monitored during the first 6-8 weeks to identify drug-related metabolic complications and opportunistic infections. Currently ART drug regimens and dosages remain the same as for the HIV-uninfected child.⁴ Further research into the optimal timing of ART introduction, choice of drug regimen as well as ART pharmacokinetics in the acutely malnourished child is needed.

WHO guidelines and prognosis

The World Health Organization has proposed a timeframe for the management of severe

malnutrition, consisting of both stabilization and rehabilitation phases. The stabilization phase addresses issues which need correction during the first 0-7 days, with hypoglycaemia, hypothermia, and dehydration requiring urgent intervention and correction.¹³ The first 24-48 hours represents a high-risk period for these complications, as well as those of various electrolyte abnormalities, and the clinician should actively seek and address these complications. During a study done in an emergency setting in Nigeria, hypoglycaemia was found to be significantly associated with death and the risk of dying within 24 hours of admission.¹⁸ A Kenyan-based study looking at the outcome of hypoglycaemia on admission found a 20% mortality rate amongst hypoglycaemic children, compared with 3.8% in normoglycaemic children.¹⁹ Mortality was particularly high in hypoglycaemic children with signs of severe malnutrition. Our study did not find hypoglycaemia at the time of presentation to be a good predictor of death, but it should be borne in mind that most of our patients had already received dextrose-containing oral, nasogastric or intravenous fluids prior to arrival at our facility as per primary management protocol, which may have affected our results.

There is minimal evidence in the literature to support a close association between hypothermia and the risk of dying. Although a common complication of malnutrition, a large study found that hypothermia on admission was neither sensitive nor specific enough to identify those at an increased risk of early mortality.²⁰ The admission temperatures of our patients were similar irrespective of clinical outcome. There was however, a 0.6 Celsius degree difference in the lowest recorded temperature during the first 72 hours of admission between survivors and non-survivors, with death more likely to occur at temperatures <35.2 degrees Celsius. Hypothermia may be an indirect marker of overwhelming sepsis.

We found documented bacteraemia to be associated with a significant increase in mortality. The majority were gram-negative organisms and the resistance spectrum indicated that many were nosocomial infections. Most children transferred from other facilities would have been on antibiotics and so the rate of bacteraemia prior to transfer could have been higher. Any child with SAM showing signs of clinical deterioration after 48 hours in any hospital setting should receive second line antibiotics to cover for nosocomial pathogens.

Metabolic complications

SAM is known to cause liver damage through mechanisms such as fatty infiltration and aflatoxin accumulation.^{21,22} Various studies looking at biochemical and histological changes of the liver have already been conducted, some dating as far back as the early 1950's.^{23,24} In our study, impaired liver function, indicated by prolonged INR and raised total Bilirubin, and hepatocellular damage (elevated ALT) were strongly associated with a poor clinical outcome. Children with SAM should be assessed for liver dysfunction and referred early if signs of significant derangement are present.

We have found that a very low serum phosphate of $<0.6\text{mmol/l}$ was associated with an increased risk of dying. Tests for serum phosphate were done at the time of admission, before feeds had been established, and thus should not be attributed to a refeeding syndrome (which usually occurs within 5 days of starting to refeed^{25,26}). This is in keeping with other studies where low serum phosphate has been associated with a higher death rate.^{27,28} This low phosphate could therefore be regarded as an additional prognostic marker and measurement of phosphate is

recommended in all patients with oedematous SAM, especially those with diarrhoea, to allow appropriate supplementation and possible referral.²⁸

LIMITATIONS

As this was a retrospective study, the collection of data has been influenced by the availability of patient records and quality of clinical record keeping. The study population was small, which may have affected statistical analysis. We have only included children with oedematous malnutrition in this study, making it difficult to compare our results with other, more inclusive, studies. Data pertaining to HIV status was incomplete thus we could not reliably make any inferences regarding the risk of dying in children affected by both HIV and oedematous malnutrition. While the WHO guidelines were followed at our hospital, information regarding clinical severity and care prior to admission to our facility was not well documented. No direct comparisons were made between patients transferred from different health facilities. Such data may be linked to the health outcomes of our patients.

CONCLUSION

Severe acute malnutrition remains a common reason for hospital admission in the under-5 year population, and is still one of the leading causes of preventable childhood deaths worldwide. Our study shows that in a tertiary setting in sub-saharan Africa, the mortality rate for children with SAM remains above the WHO target. Factors contributing to the high mortality include young

age (<12 months), a delay in presentation, and HIV infection. The WHO guideline now includes aspects of managing the HIV-infected malnourished child and addresses issues such as ART initiation, drug dosages and feeding strategies.

The first 72 hours of management are crucial as this is when the risk of dying is greatest. The WHO guideline remains a valuable tool in managing patients with SAM during this high risk period. However, our study suggests that there may be additional prognostic factors applicable to patients at a referral hospital and we propose that these be considered in future management strategies.

We have found a significant difference in the mortality rates of children transferred from level 1 or 2 hospitals compared to those transferred from a primary health care facility. This can be accounted for by a difference in the time taken for very sick children to receive more specialized care. This suggests that improved clinical guidelines are needed to help identify patients not responding to treatment in order to hasten transfer to a specialist unit.

We are hopeful that the findings and recommendations of this study will make a significant contribution towards lowering the mortality rate for SAM to <5%, in keeping with the WHO target.

RECOMMENDATIONS

General recommendations:

- 1 Adhere to standard WHO 10 steps, with emphasis on temperature regulation, glucose control, fluid management and treatment of sepsis.
- 2 Establish guidelines to assist in the identification of high risk patients.
- 3 All children with SAM should have HIV status documented, and should be considered for anti-retroviral treatment where indicated.
- 4 Further research is needed to determine the best time to institute anti-retroviral therapy in severely malnourished children.
- 5 Further prospective studies are needed to identify risk factors for increased mortality.

Recommendations for primary health care clinics / district hospitals:

- 1 High risk patients should be transferred early for more specialized care.
- 2 At primary care level, recognition and appropriate management of growth faltering must be optimized.

Recommendations for secondary / tertiary level hospitals:

- 1 Aggressive treatment for nosocomial sepsis should be instituted in any inpatient with clinical deterioration after 48 hours of hospitalization

- 2 Any very ill child should have liver biochemistry and phosphate levels checked with awareness of implications of results.

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