UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

EFFECT OF BACTERAEMIA AND HIV INFECTION ON TREATMENT OUTCOME IN CHILDREN WITH SEVERE ACUTE MALNUTRITION ADMITTED TO THE UNIVERSITY TEACHING HOSPITAL MALNUTRITION WARD, LUSAKA, ZAMBIA

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A dissertation submitted in partial fulfillment of the requirement for the award of the degree of Masters of Medicine in Paediatrics and Child Health.

DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or at any other University.

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APPROVAL

This dissertation of Dr. Mwate Mwambazi-Mweene is approved as fulfilling the requirement for the award of the degree of Masters of Medicine in Paediatrics and Child Health by the University of Zambia.

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DEDICATION

I dedicate this work to my late mum, Mrs. Elizabeth Mwambazi Hanankuni, for her unmatched effort in teaching me the culture of hard work, my beloved husband and best friend Morgan, on whose shoulders I have bravely relied on, and to my sons, Simon, Chitebula and Morgan Jr, for their support and love.

ACKNOWLEDGEMENTS

I wish to thank the following for their great contribution towards this project;

My supervisor, Prof Chifumbe Chintu, for all the academic and technical support rendered during the development and completion of this project; my co-supervisor, Dr Veronica Mulenga, for the guidance through proposal development and study methodology.

Dr Lukwesa Chileshe and Mr Darlington Mwape for providing excellent laboratory support; Hamond, Andalek and Mutinta for their dedication as research assistants.

Dr Able Irena for technical support in data analysis and interpretation.

Vanderbilt University grant and FANTA-2 through Valid International for the financial support for this project.

My Heartfelt gratitude goes to mothers/guardians and children who took part in this study, without whom this study would not have taken place.

LIST OF ACRONYMS

CMAM	-	Community Management of Acute Malnutrition
CTC	-	Community Therapeutic Care
IQR	-	Interquartile Range
OTP	-	Outpatient Therapeutic Program
PICT	-	Provider Initiated Counseling and Testing
RUTF	-	Ready-to-Use Therapeutic Food
SD	-	Standard Deviation
SE	-	Standard Error
SAM	-	Severe Acute Malnutrition
UN	-	United Nations
UTH	-	Zambian University Teaching Hospital
WHO	-	World Health Organization
WHZ	-	Weight for Height Z score

TABLE OF CONTENTS

List of figures

List of tables

1. ABSTRACT

Background

Severe malnutrition remains a major cause of mortality in children less than 5 years at the University Teaching Hospital, with rates ranging between 30-40 % among patients admitted in the malnutrition ward. The effects of bacteraemia and HIV infection on outcome to treatment remain unknown.

Objective

To establish the magnitude of bacteraemia and HIV infection in children with severe acute malnutrition (SAM) admitted to the Zambian University Teaching Hospital (UTH) malnutrition ward, describe the types of bacteria and antimicrobial sensitivity, and effect on treatment outcome.

Method

Children admitted to the malnutrition ward at the UTH from August to December of 2009 were included in the study after acquiring informed consent. Data on nutritional status, social demographic factors and admission medical conditions were collected. In addition blood sample was collected from every child. Identification of positive culture yielding pathogenic bacterial strains were done using BACTEC machine, and completed with morphologic and biochemical tests. Antibiotic susceptibility tests were performed using Kirby-Bauer susceptibility testing method.

Results

Data were collected from 441 children aged six to 59 months old, 55.3% (244/441) of whom were boys. Median age of the cohort was 17 months (inter quartile range, IQR 12-22). 68.9%

(295/428) had edema at admission; 57.4% (247/430) had weight for height Z score < -3SD at admission. The majority, 67.3% (261/388) of the children presented with diarrhea. 38.9 % (162/420) tested HIV-positive; 21.4% (91/425) of the children had one or more bacteria isolated from their blood samples; 40.5% (174/430) of the children died. The predominant organisms isolated were *Coagulase negative Staphylococcus (20.7%), E. coli (15.5%), Staphylococcus aureus (15.5%), Salmonella (12.1%), Pseudomonas (8.6%), Diphteriods (6.9%) and Klebsiella pneumonia (6.9%).* Crystalline Penicillin had 85.7% (12/14) resistance; ranging from 66.7% to *S.Aureus* to 100% to *E.coli* and *klebsiella.* Gentamycine had 23.6% (5/19) resistance; ranging from 0% to *E.coli* to 100% to *Klebsiella;* Ciprofloxacin had 27.9% (13/43); ranging from 0% to *Salmonella, Klebsiella* and *Psuedomonas* to 55.6% to *E.Coli.* HIV positive children had increased odds of mortality, adjusted OR= 1.70 (95% CI 1.04-2.83, P=0.04). Children with bacteremia had increased odds of mortality compared to those with no bacteremia, adjusted OR=1.90 (95% CI 1.04-3.40, P=0.04). There was no interaction between bacteremia and HIV infection on outcome (P=0.77).

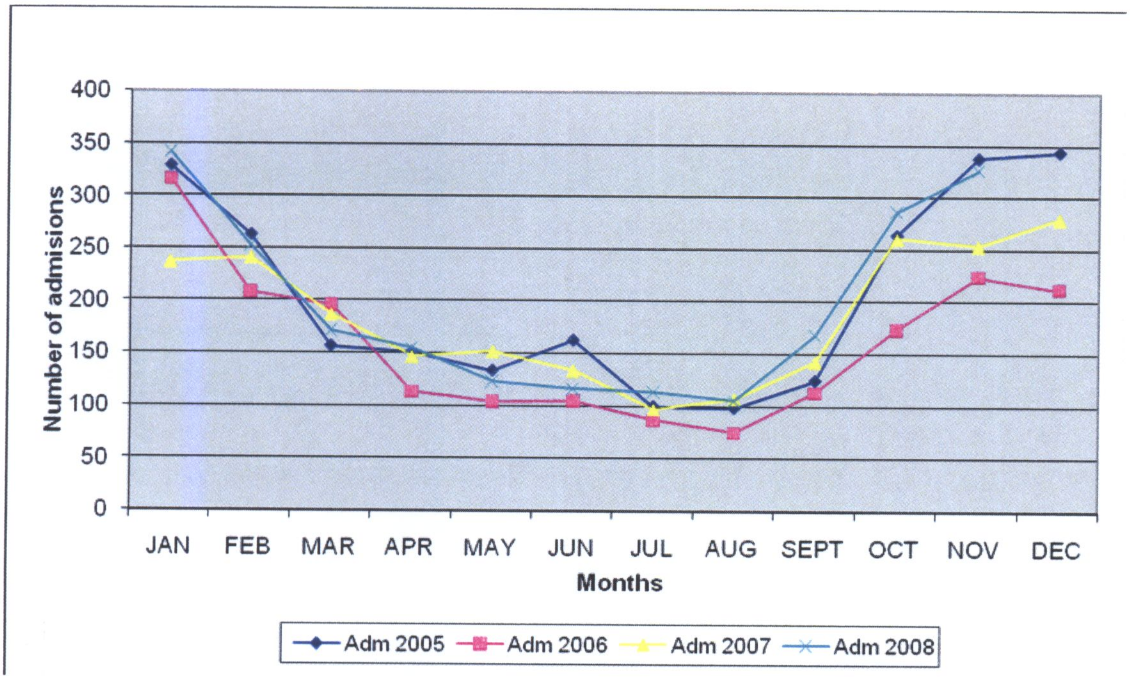
Conclusion

SAM children admitted in UTH suffer from high prevalence of bacteremia on admission. This has increased their odds of death by almost two folds regardless of their admission nutritional status, diarrhea, age, sex, and HIV status. The baseline mortality and HIV prevalence in the malnutrition ward was higher than other similar studies. The drug resistance, to first line antibiotics mainly to penicillin, calls for an in-depth review of drug management.

2. BACKGROUND

With stricter adherence to the WHO therapeutic guidelines mortality of children with SAM is suggested to be lower than 5% [1]. However, the mortality rate of children with SAM in inpatient treatment units has remained unacceptably high [2]. Such high mortality in inpatient units have been attributed to either co-morbidity such as HIV infection and/or to poor adherence to the WHO therapeutic guidelines [1]. Similarly, the mortality rate of SAM children in UTH malnutrition ward is very high ranging between 30-40% [3]. This is despite efforts made to reduce child mortality in the unit through training on inpatient management of severe malnutrition as per the WHO recommendations [4] since 2001. Management of children with SAM in the ward is challenged by overcrowding (often more than one child receives treatment per cot, especially during the peak malnutrition period which occurs during the rainy season) high HIV prevalence, late presentation, staff turnover, critical shortage of nursing staff, and occasional shortage of therapeutic supplies. The peak malnutrition season is between October and March.

Figure 1 Monthly admission at UTH malnutrition ward by year



The bacteraemia pattern in children with SAM receiving treatment in the ward is not known as no study has been conducted. Bacteraemia is known to occur frequently in malnourished children and carry high case fatality [2, 5, 6, 7]. Current first line antibiotics used for treatment of children with SAM in the malnutrition ward is a combination of Crystalline Penicillin and Gentamycin. Chloramphenical or Cefotaxime is used as a second line drug, with Cefotaxime being the drug of choice. Ciprofloxacillin is used as third line drug. High resistance patterns to these drugs have been documented in severely malnourished children in previous studies [2, 5, 6, 7].

Despite routine administration of antibiotics to all children in the ward, case fatality remains unacceptably high. The role of bacteraemia in a background of such a high mortality is not studied and raises a concern. HIV infection in SAM children is also known to decrease their survival [8, 9]. Therefore this study was conducted to identify the prevalence of bacteraemia and assess the relationship between HIV infection, bacteraemia and the treatment outcome.

3. LITERATURE REVIEW

Acute malnutrition is a devastating public health problem of epidemic proportions. It is one of the leading causes of morbidity and mortality in childhood. Worldwide, some 55 million children under the age of five suffer from acute malnutrition and over 19 million of these from the most serious type – severe acute malnutrition. Every year, 5 million children die of malnutrition [8, 10].

Severe malnutrition is defined as weight for height z-score <-3SD, bilateral oedema of kwashiorkor, or mid-upper arm circumference (MUAC) <11.0 cm [11].

Malnutrition may be due to improper or inadequate food intake or may result from inadequate absorption of food. The types of malnutrition mainly referred to are;

- Marasmus which is mainly due to insufficient food, inadequate knowledge of feeding techniques or poor hygiene. The features are those of protein and calorie deficiency.
- Kwashiorkor is mainly due to deficiency of proteins. Poverty and famine, ignorance and poor maternal nutrition are among the major contributory factors.

Pre-school aged children in developing countries are often at risk of malnutrition because of their dependency on others for food, increased protein and energy requirements, and immature immune system [12, 13].

The human body needs energy and nutrients to function. If food intake is inadequate, the body begins to break down body fat and muscle, the metabolism begins to slow down, thermal regulation is disrupted, the immune system is weakened and kidney function is impaired.

Because children are growing, they must consume enough nitrogenous food to maintain a positive nitrogen balance, where as adults need only maintain nitrogen equilibrium [12].

Bacterial infections occur frequently in malnourished children and carry high case fatality [6].This is because malnutrition brings greater susceptibility to infections and tends to increase risk of mortality from septiceamia due to disturbance in the normal immune mechanism. There is evidence that immunological deficiency results from protein energy malnutrition (PEM). A similar pattern of infection is encountered in the post-measles state. Measles depresses the cell-mediated immunity, and a synergistic effect of measles and PEM could account for the bad prognosis when these conditions coexist [5, 6].

In 1959 Smythe and Campbell drew attention to the high incidence of septiceamia in kwashiorkor and pointed out the very high mortality rate in such patients. They concluded that the frequency with which intestinal bacteria were found, and breaks in the intestinal barrier might account for the high incidence of septiceamia. It was also postulated that there was a disturbance in the normal immune mechanism which destroys any intestinal bacteria gaining entrance to the blood stream. Their study supported earlier evidence that infection was the most important cause of death in kwashiorkor [12].

In East Africa, where malnutrition is increasing in prevalence and is becoming a serious public health problem affecting about 5% of under five children, it was discovered that the ability of malnourished child to handle infections is lower. Common infections were those caused by Streptococcus pneumonia, Klebsiella pneumonia, Escherichia coli and Haemophilus influenza. Malnutrition and infections are interrelated [13].

The contribution of septiceamia to mortality in children with malnutrition has long been known and is still being defined. It is commonly not recognized in severely malnourished children and may develop rapidly; thus, it may be difficult to detect in a busy paediatric ward in Africa, and hence the practice of treating all severely malnourished children with antibiotics [4, 14]. However, with continued use of antibiotics, resistance to the commonly used drugs has immerged. A study conducted in Nigeria showed that S. aureus and gram negative rods (pseudomonas species and coliform) are the leading causes of septiceamia in children, a pattern similar to other low income countries. These were highly susceptible to third generation Cephalosporins (namely Ceftazidine, Cefuroxime and Ceftriazone) and Azithromycin [15].

In sub-Saharan African countries with the highest case fatality of malnutrition, AIDS and tuberculosis (TB) have led to an epidemic of secondary severe malnutrition related to these co-morbidities. Severely sick malnourished children with AIDS and TB appear to differ in their pathophysiological response to the accepted WHO therapeutic guidelines, compared to children with primary severe malnutrition due to food shortage and non HIV/TB related infection [16, 17, 18].

This has lead to a change in antibiotic sensitivity patterns to common bacteria in the HIV era. In South Africa, 50% of S. pneumonia isolates from HIV infected children were penicillin resistant compared to 23% of HIV negative isolates [9]. Hannif et al found that bacteraemia affected 1 in every 6 severely malnourished children and carried high mortality especially among the HIV-positive [6].

The target of Millennium Development Goal 4 is to "Reduce by two thirds, from 1990 to 2015, the under-five mortality rate". Efforts to improve child survival can be effective only if they are based on reasonably accurate information about the causes of childhood deaths. Cause-of-death information is needed to prioritize interventions and plan for their delivery, to determine the effectiveness of disease-specific interventions, and to assess trends in disease burden in relation to national and international goals [10]

4. STATEMENT OF PROBLEM

The prevalence of severe malnutrition in Zambia was very high where five percent of children are wasted according to the Zambia demographic health survey 2007.This could be attributed to the poor social economic status that most Zambians were in.
Morbidity and mortality rates were unacceptably high being at over 40%. In the fourth quarter of 2008, out of 886 admissions, 358 were discharged while 368 died (41.5%) according to UTH, Dept of Peadiatrics records.

4.1 Study Justification

There was no latest data about the prevailing situation at that time on common infections and sensitivity patterns among severely malnourished children at the University Teaching Hospital. It was also not known how the HIV era had remodeled the pattern of infecting bacterial organisms and their sensitivity to commonly used antibiotics. This had created a knowledge gap on the prevailing pattern of bacterial infections among severely malnourished children presenting to the University Teaching Hospital.

A study that was done earlier in severely malnourished children presenting with persistent diarrhea at UTH found that 17% had positive blood cultures [3]. However this study targeted only those malnourished children with persistent diarrhoea.

The aim of the study therefore, was to define the prevailing pattern of bacterial infections in severely malnourished children, and how this pattern had been influenced by HIV. It was also hoped that the information gathered would possibly influence policy on the management of these children.

Results from the study were to help care givers to precisely and adequately manage these children, thereby reducing on cost incurred when using antibiotics that were inefficient due to resistant microbial agents. There would also be a reduction in hospital stay and subsequently reduced mortality.

The knowledge of common microbial organisms and the appropriate antibiotic use would then help in reducing mortality due to bacteraemia and hence may contribute to the attainment of the fourth millennium development goal, which is to reduce the under-five mortality rate by two thirds, between 1990 and 2015 [19].

5. MAIN OBJECTIVE

The aim of the study was to describe the effect of bacteraemia and HIV infection on treatment outcome among children presenting with severe malnutrition at the University Teaching Hospital.

5.1 Specific Objectives

1. To determine the presence of bacteraemia and the common organisms isolated in severely malnourished children presenting at UTH.
2. To determine the antibiotic sensitivity pattern among the bacterial infections in severely malnourished children presenting at UTH.
3. To determine the effect of HIV status on treatment outcome in severe malnutrition and bacteraemia.

6. METHODOLOGY

Recruitment Inclusion Criteria

1. Children with severe malnutrition; weight for height giving SD score equal or less than -3 and/or presence of oedema.
2. Age of 6 to 59 months
3. Consent to enroll into the study given by parents or guardians.

Recruitment Exclusion Criteria

1. Lack of consent.

Sample Size

The study was carried out over a period of five months.

Using a prevalence study formula;

$$N = \frac{(1.92)2\ P(1-P)}{D2}$$

N- Sample size

P- Estimated prevalence. In this case, 16% was used.

D- p value (0.05)

At 95% confidence level, N=416.

Assuming 85% response, 489 is the total size.

Ethical considerations

Ethical clearance was sought from the Research Ethics Committee of the University Of Zambia (REC). And a written consent was obtained from the parents /or guardians. Permission to do the study was also sought from the managing director of the University Teaching Hospital.

The purpose and procedures were fully explained to the parents and guardians, in a language that they fully understood and the results of the investigations were made available and explained to them as soon as they are ready.

Procedure

Children admitted to the UTH malnutrition ward were eligible to be enrolled into the study which took place between August and December 2009. A total of 491 children admitted, aged between six to 59 months were included in the study after informed consent was obtained. Children were admitted to the ward based on presence of bilateral pitting edema, and/or WHZ score less than minus three standard deviations (NCHS).

Nutritional status of the children was measured by trained ward attendants. Height was measured using stadiometer, a device used to measure height of patient either standing or lying down. The attendants were trained on how to use the stadiometer and to get patient's height or length to the nearest cm. Weight was measured using UNISCALE to the nearest 100gm. Bilateral pitting edema was assessed and graded as: "no edema", "+" if edema on both feet, "++" if edema up to both legs, or "+++" if generalized edema. Using structured questionnaires social demographic data were collected. These included age, educational status, and occupation status of the mother/guardian.

6.1 Blood culture and sensitivity:

A blood sample was taken from all 441 children. Stoppered test tubes, where blood sample can only be injected or drawn from the tube with a syringe, were used to collect and transport blood in order to minimize sample contamination. Five milliliters of blood was withdrawn from a peripheral vein under aseptic conditions after cleaning the skin with 70% alcohol and two percent tincture of iodine. The blood specimen was transported to the laboratory in a blood culture media pre-sealed in the test tubes. Two milliliters of blood was put in an EDTA bottle for full blood count and the rest used for blood culture study.

Culture bottles yielding positive pathogenic bacterial strains were identified using BACTEC machine. The positive yielding specimens were then cultured. Gram's stain was done and inoculation made on to 7% sheep blood, chocolate and MacConkey agar. The plates were then incubated at 37°C for 18 – 24 hours. Blood and chocolate agar plates are incubated under carbon dioxide.

Culture isolates were identified according to standard methods. For Gram negatives, serological identification of salmonella species and coagulase test for *Staphylococcus aureus*, Optochin for *Streptococcus pneumoniae* and X and V factors for *Haemophilus influenza* was done. The Kirby-Bauer diffusion method was used to test the susceptibility to the isolates on Muller-Hinton Agar-2. Commonly prescribed antibiotics were tested and graded as sensitive or resistant. Resistance was defined by the zone diameter below that given in standard operating procedure in accordance with the CLSI (Clinical Laboratory Standards Institute) 2005.

6.2 HIV testing

HIV testing was made through a Provider Initiated Counseling and Testing (PICT) approach. HIV serology using Determine HIV ½ test and/or DNA PCR (for a child under 18 months old with a positive HIV serology) were done after parental consent was obtained. Blood for HIV testing was collected separately from the blood culture as children and their guardian needed to be counseled beforehand.

6.3Diagnosis and management

Children were managed by a team of physicians comprising of three rotating resident physicians (average stay in the ward of 4 months) and two junior resident medical officers, supervised by one senior registrar and one consultant paediatrician. In addition, three to five nurses attend to the children in the ward (number varying depending on the time of the day). The ward has 59 beds. During the study period a peak admission of 112 children in a day was recorded.

On admission, all children were examined by the attending physicians. Clinical evaluation was done to assess co-morbidities. Fever was defined as admission axillary temperature of greater than 37.5°C. Diarrhea was diagnosed based on history (mothers/guardian assessment) of three or more loose stools a day.

Children were managed using WHO standard guidelines for the management of severe malnutrition [4]. Routine antibiotics (Crystalline Penicillin and Gentamycin) were given intravenously on admission. These drugs were substituted by second or third line antibiotics in situations where a child's condition failed to improve or even deteriorated. Drugs used as second line in the unit were Cefotaxime, or any other third generation cephalosporin; or Chloramphenical. Third generation antibiotic available was Ciprofloxacillin. Children were given oral vitamin A on admission (200000 IU if ≥12 months or 100,000IU if <one year); those with signs of Vitamin A deficiency received further doses on day two and eight. Children with

diarrhea were given ReSoMal (Rehydration Solution in Malnutrition). ReSoMal is a modified rehydration solution suitable for children with malnutrition. A nasogastric tube was inserted into children who were assessed to be too sick to feed voluntarily or those with persistent vomiting. Children received 10% Dextrose upon admission. Intravenous fluids (often ½ strength Darrow's solution) were used for management of shock or in children with persistent diarrhea with dehydration.

F75 was used in the first phase of treatment. F75 is a special therapeutic feed used in the initiation phase of nutritional rehabilitation in children with severe malnutrition. Each 100mls of F75 contains 75 calories. After stabilization, the F75 is replaced by F100, whose calorie content is 100 per each 100mls. These therapeutic feeds are commercially prepared, and are also prepared using fresh or fermented milk on the ward. The latter was especially encouraged for those children who continued to have diarrhea after admission. During second phase children were either treated with Ready-to-Use Therapeutic Food (RUTF) or F100. RUTF is a peanut based feed.

The outcome of the children in the study included those who exited from the unit as "recovered" (child able to consume RUTF and referred to one of the 25 outpatient therapeutic programs (OTP), or until the child achieved WHZ>-1SD & no edema especially those children who failed to develop appetite for RUTF). Others were "absconders" (child absent from the unit for two consecutive days) while others left against medical advice (LAMA) (if child is taken home against medical advice). Other children died while in the unit. Four of the participants were transferred to AO5 the isolation ward for either tuberculosis or measles

7. Data Analysis

Data were initially checked for inconsistencies and missing values. Missing values for admission data were generally minimal. Missing values were excluded from respective analysis. After eliminating the patients with missing values, 441 patients were included in the analysis.

Variables in the dataset included binary (sex, HIV, fever, WHZ score <-3SD, and diarrhea) and categorical data (blood culture, nutritional status, admission edema and outcome). Weight, height, age were numeric data. However, for analysis purpose these were grouped as categorical data. During the analysis, a variable called "nutstat" was created based on a combination of child's admission edema and WHZ score. Accordingly, children were grouped into one of these groups "Marasmic-Kwash", "Kwashiorkor" or Marasmus".

Two models were developed for analysis; one with outcome data coded as binary (Alive and dead) and another outcome data coded as categorical (cured, death, absconded, left against medical advice, and transfer out to isolation paediatric ward). A model with outcome as dependent variable and another one with blood culture as a dependant variable were used. Exposure factors; being HIV positive, having a particular nutritional status (Marasmus, Marasmic–Kwashiorkor, or Kwashiorkor), diarrhea, fever, age and sex were used in each model. Power of the study was estimated retrospectively for the association of blood culture and HIV with outcome, and HIV with blood culture.

Difference in mean values was assessed using t-test or ANOVA where applicable. Mean with standard deviation (SD) or median and IQR were calculated and reported. Logistic regression

Difference in mean values was assessed using t-test or ANOVA where applicable. Mean with standard deviation (SD) or median and IQR were calculated and reported. Logistic regression was used to assess prognostic value of the HIV infection, and admission bacteremia. Univariate and multivariate analysis was done by adjusting for edema, sex, HIV, WHZ score, nutritional status, blood culture, and age. Logistic regression was chosen to enhance comparability of this study with previous studies. Risk of mortality was expressed as odds ratio. Likelihood ratio test and associated P-values were used to test association. Adjusted and un-adjusted odds ratio, 95% confidence interval and P-values were calculated and reported. Analysis was done using STATA 9.

8. RESULTS

8.1Age and Sex distribution

A total of 441 children were enrolled in the study. Majority, 55.3% (244/441) were boys. A quarter of the enrolled children (101/441) were in the age group six to 12 months old. Median (IQR) age of the cohort was 17 (12-22) months. There was no significant difference in age between boys and girls (P=0.8).

Table 1 Age and sex distribution

Age group	Girls		Boys			
(months)	#	(%)	#	(%)	Total	(%)
6-11.9	55	(27.9)	46	(18.9)	101	(22.9)
12-17.9	56	(28.4)	78	(32.0)	134	(30.4)
18-23.9	46	(23.4)	71	(29.1)	117	(26.5)
24-59.9	40	(20.3)	49	(20.1)	89	(20.6)
Total	197		244		441	

8.1 Clinical presentation on admission

Over half, 68.9% (295/428), of the children had edematous form of malnutrition at admission, whereas, 57.4% (247/430) of the children had WHZ less than -3SD. Based on a combination of these two criteria, 28.2% (116/411) had marasmus, 39.7% (163/411) had kwashiorkor, and 32.1% (132/411) had marasmic-kwashiorkor. Admission weight of the children ranged from 3.2 Kg to 15.5 Kg, with a median admission weight of 6.5Kg (IQR=5.5 –7.9). The boys, mean (SD) 7.0(1.6) Kg, were heavier than the girls, mean (SD) 6.6(2.1) Kg at admissions, (P=0.02).

Data on diarrhea at admission was available for 88% (388/441) children. Of these, 67.3% (261/388) had diarrhea at admission. HIV test result was available for 95.2% (420/441) of the children. The HIV prevalence was 38.6% (162/420).

8.2 Bacteraemia and common organisms

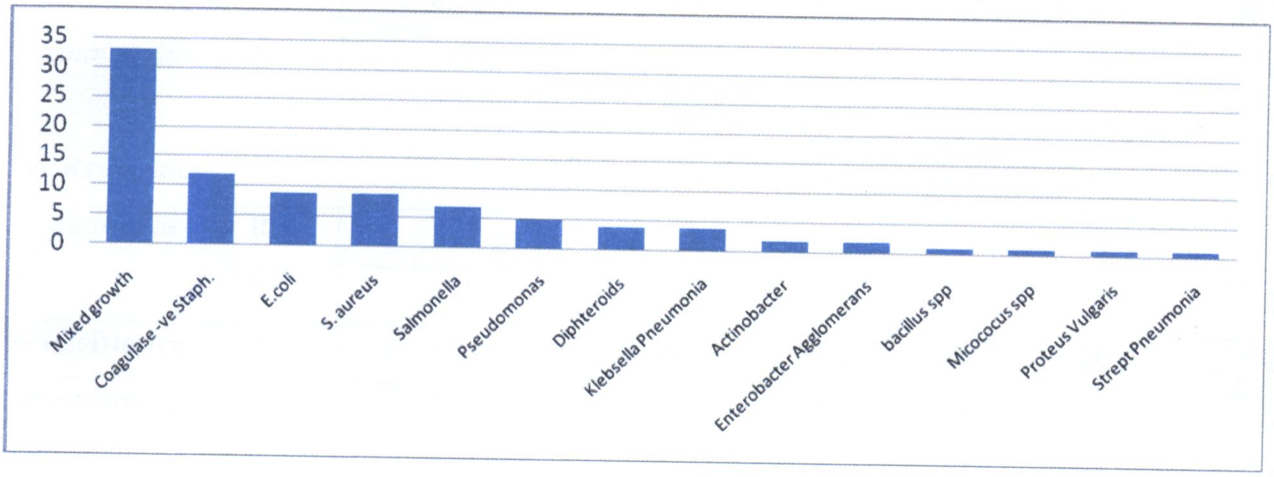
Admission blood culture result was acquired for 96.4% (425/441) children. Prevalence of bacteraemia was found to be 21.5(91/425). Single bacterial growth was found in 13.7% (58/425) of the children. On the other hand, 7.8% (33/425) had mixed bacterial growth. Difference in prevalence of bacteremia between HIV-positive, 21.2% (33/156), and HIV-negative, 20.8% (52/250), was not statistically significant (P=0.9). One patient was treated for Tuberculosis based on clinical presentation even though gastric lavage for Acid Fast Bacilli was negative. The

Sensitivity of microscopy and culture for gastric lavage ranges from 0% to 13% (median 7%) [20]

Table 2 Admission bacteremia pattern

Blood culture result at admission	#	%
No growth	334	78.6
Single growth	58	13.7
Mixed growth	33	7.8
Total	425	100

Figure 2 Number of blood culture result by type of organism isolated



Excluding the mixed growth groups, *Coagulase negative Staphylococcus* was the predominant *(20.7%)* organisms identified, followed by *E. coli (15.5%), Staphylococcus aureus (15.5%), Salmonella (12.1%), Pseudomonas (8.6%), Klebsiella pneumonia (6.9)* and Diphteriods (6.9%) (Figure 2)

8.4 Sensitivity patterns

Table 3 Drug resistance pattern by selected isolates

ISOLATES	Drug test	PENICILLIN	GENTAMYCIN	CEFOTAXIM	CHLORAMPHENICOL	COTRIMOXAZOL	CIPROFLOXACIN
E.Coli	R	2	0	4	2	7	4
	S	0	5	4	6	0	5
Resistance (%)		100	0	50	25	100	55.6
S.Aureus	R	2	ND	4	2	5	3
	S	1	ND	4	4	2	4
% Resistance		66.7		50	33	71.4	42.8
Coagulase –ve ***Staphylococcus***	R	5	1	6	4	13	3
	S	1	0	4	9	1	8
% Resistance		83.3	100	60	30.8	92.9	27.3
Salmonella	R	ND	0	0	1	1	0
	S	ND	1	5	6	4	7
% Resistance			0	0	14.3	20	0
Klebsiella	R	1	3	2	1	1	0
	S	0	0	1	0	1	2
% Resistance		100	100	75	100	50	0
Pseudomonas	R	ND	1	1	0	0	0
	S	ND	3	3	1	1	3
% Resistance			25	25	0	0	0

ND=Not Done, -ve=negative, R=resistance, S=sensitive

*the table above only shows isolates of greater importance and not all resistance results are included

Crystalline Penicillin had an overall resistance of 85.7% (12/14) resistance; ranging from 66.7% to *S.Aureus* to 100% to *E.Coli* and *klebsiella.* Gentamycin had 23.6% (5/19) resistance; ranging from 0% to *E.coli* to 100% to *Klebsiella;* Ciprofloxacin had 27.9% (13/43); ranging from 0% to *Salmonella, Klebsiella* and *Psuedomonas* to 55.6% to *E.Coli* (Table 3).

8.5 HIV in children with Severe Malnutrition

HIV test result was available for 95.2% (420/441) of the children. The HIV prevalence was 38.6% (162/420). The patients without the HIV test were mainly those who died before the PITC (Provider Initiated Counseling and Testing) was offered to them.

8.6 Treatment outcomes

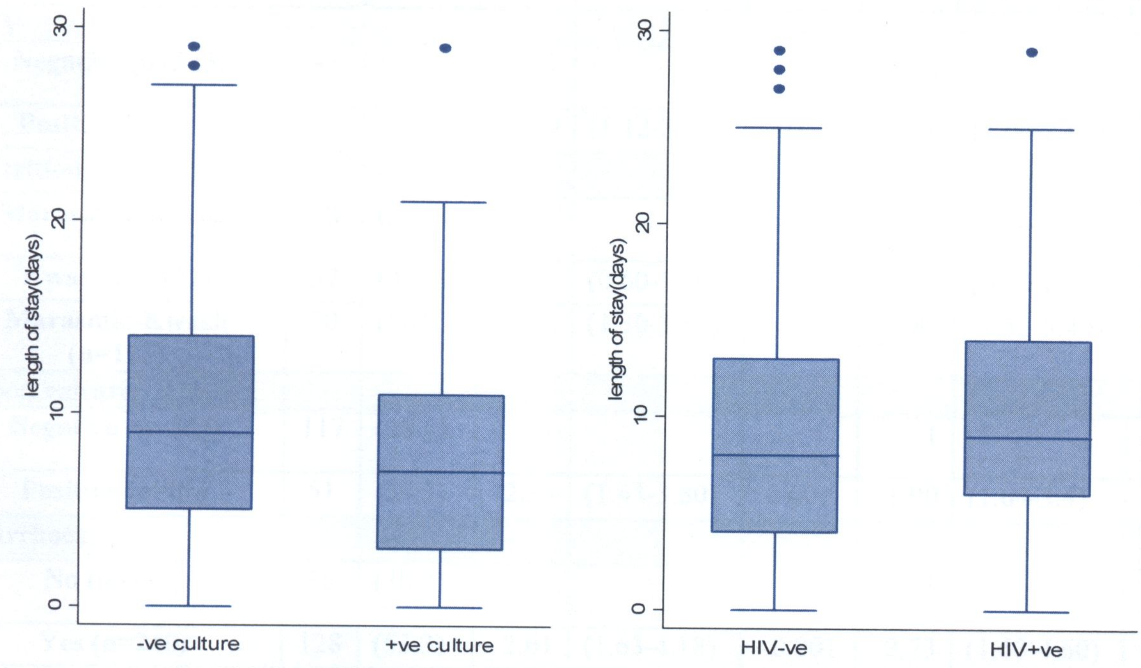
Table 4 Blood culture isolates and treatment outcome

Isolates	Cured	died	Death (%)
E.coli	0	8	100
S. Aureus	4	6	60.0
Coagulase –ve *Staphylococcus*	7	4	36.4
Salmonella	3	4	57.1
Klebsiella	1	3	75.0
Pseudomonas	4	1	20.0
Total	19	26	57.8

Children with *E.coli* bacteremia had the highest risk of death 100% (8/8), followed by children with *Klebsiella* infection, 75% (3/4). Children with Coagulase negative *Staphylococcus* bacteremia had the lowest risk of mortality, 36.4% (4/11) (Table 4).

The median length of stay for recovered children was 10 days (IQR=7-15, range 0-65). The median length of stay for those children who died was 5 days (IQR=2-10, range 0-61). Of those children who died, 30.6% (53/173) died within 48 hours of admission; 65.3 %(113/173) had died within one week of admission. Children with bacteremia stayed for less days, mean of 8.5 days, than those without bacteremia, mean of 10.9 days, (P=0.02). HIV-positive children stayed, mean (SD) of 11.9(9.4), more than HIV-negative children, mean (SD) of 9.4(7.6), (P=0.004) (Figure 3).

Figure 3 Box plot for length of stay by blood culture and HIV status *



****length of stay restricted to less than 30 days to exclude outliers***

Of the exits, 53.7% (231/430) were discharged recovered; 40.5% (174/430) died and 4.0% (17/430) absconded. Six children referred to isolation ward because they were diagnosed with tuberculosis and two children left against medical advice.

Table 5 Crude and adjusted odds ratio of outcome

	Outcome (died)		Crude OR		P-value	Adjusted OR (95% CI)*		P-value
	#	(row %)	(95% CI)		(trend)			
Sex								
F (n=179)	81	(45.3)	1					
M (n=226)	93	(41.1)	0.85	(0.57-1.26)	0.4			
Age group, months								
6-11.9 (n=92)	47	(51.1)	1			1		
12-17.8 (n=123)	58	(47.2)	0.85	(0.50-1.47)		0.77	(0.39-1.50)	0.4
18-23.9 (n=111)	38	(34.2)	0.49	(0.28-0.88)	0.06	0.39	(0.19-0.77)	0.007
24-59.9 (n=79)	31	(39.2)	0.62	(0.34-1.14)		0.66	(0.31-1.37)	0.3
HIV								
Negative (n=243)	91	(37.5)	1			1		
Positive (n=149)	75	(50.3)	1.69	(1.12-2.56)	0.01	1.70	(1.04-2.83)	0.04
Nutritional status								
Marasmus (n=102)	38	(37.3)	1			1		
Kwash (n=152)	57	(37.5)	1.01	(0.60-1.70)	0.002	1.37	(0.75-2.53)	0.31
Marasmic-Kwash (n=123)	70	(56.9)	2.2	(1.30-3.80)		2.87	(1.52-5.40)	0.001
Blood culture								
Negative (n=304)	117	(38.5)	1			1		
Positive (n=86)	51	(59.3)	2.33	(1.43-3.80)	0.001	1.90	(1.04-3.4)	0.04
Diarrhoea								
No (n=115)	35	(30.4)	1			1		
Yes (n=240)	128	(53.3)	2.61	(1.63-4.18)	<0.001	2.73	(1.60-4.60)	<0.001

Adjusted for HIV, blood culture and diarrhea & vomiting. OR=odds ratio, CI= confidence interval

HIV infection, positive blood culture and diarrhoea increased odds of death by twofold.

Sex, admission hemoglobin, and fever had no effect on survival (P>0.2). HIV infection was independently associated with survival after adjusting for bacteremia, age group, admission nutritional status and admission diarrhea, adjusted OR=1.70 (95% CI 1.04 – 2.83, P=0.04). Blood culture increased the odds of death by almost two fold independent of HIV infection, age group, and admission diarrhea and nutritional status, adjusted OR= 1.90 (95% CI 1.04 – 3.4, P=0.04). There was no interaction between bacteremia at admission and being HIV-positive on treatment outcome (P=0.15).

Fever at admission, sex, age of the child, and HIV status were not associated with presence of bacteremia in the children (P>0.2). Diarrhea at admission was positively, OR= 2.0 (95% CI 1.1-3.6, P=0.03), associated with presence of bacteremia.

The estimated power for the relationship between HIV and outcome was 67.1%, and bacteremia and outcome was 91.5%. For the relationship between HIV and bacteremia, the estimated power was 2.8%.

9. DISCUSSION

9.1Age and sex distribution

The age of the children in the study is comparable to the studies done by Bachou et al. and Sunguya et al, with majority of affected children being between ages 12months to 24 months. However, children in the study by Maitland K et al. were older (median age of 25 months, IQR 16-46).

9.2 Clinical presentation

Predominant (68.9%) form of malnutrition in this study was kwashiorkor. The study by Maitland K et al., however, had lower prevalence of kwashiorkor as compared to marasmic-kwashiorkor (42%) [2]

High prevalence of diarrheoa on admission was found in this study. In a similar manner, a high prevalence of diarrhea has been documented in previous studies [5, 21, 22]. Such co-morbidies could partly be explained by the poor sanitary conditions and poor water supply in the community from where the children came from. Admission rate in the ward normally peaks during rainy season which is often associated with high cases of diarrheal diseases in Lusaka [23].

9.3 Bacteremia and survival of SAM children

A total of 91 children had bacteremia at admission indicative of community acquired infections. The prevalence of bacteremia was 21.4% (91/425). This was higher than other studies done in similar groups of children [2, 5, 14, 30]. HIV infection was not found to be a risk factor for the presence of bacteremia at admission, nor age group, or sex. This compares favorably with

Bachou et al., 2006 study. Diarrhea at admission was strongly associated with presence of bacteremia. This could be indicative of bacterial translocation from the intestine [12]. Gram negative bacteria are more commonly translocate into blood stream, and this could explain the higher mortality among children with gram negative sepsis.

Children with bacteremia at admission had increased risk of mortality compared to those with no bacteremia (58.4% vs 38.2% respectively), similar to studies by Reed at al. & Maitland et al. However, this finding is in contrast to Bachou et al. & Bahwere et al. studies. In addition to the mortality rate reported in these two studies being lower, no significant difference in mortality by bacteremia was detected [5, 30].

9.4 Drug Sensitivity

The microorganisms identified from blood culture reflect of community acquired infections as blood sample was taken within a day of admission to the ward. Similar pattern of pathogens were isolated from blood samples of children with SAM [9, 30]. It is not clear why children with E.coli bacteremia had the highest mortality in this study despite E.coli being found to be sensitive to Gentamycin. Since analysis is not done by type of antibiotics use, much cannot be said on this at this stage.

While the resistance pattern for Gentamycin was lower, Crystalline Penicilline had a higher resistance pattern to the commonest organisms isolated. A lower resistance pattern was found for Ciprophloxacin, which is the third line treatment at the moment. There was high resistance to Cotrimoxazole by the commonest organism isolated similar to other studies [5]. In vitro drug sensitivity patterns have been observed to differ from expected treatment outcome in children with severe malnutrition [30, 31]. Pathophysiological changes that are common in such children are thought to affect the drug absorption and pharmacokinetics, possibly explaining the disparity between in vitro drug sensitivity patterns and treatment outcome [31]. A study to investigate the appropriate combination and dosage of antibiotics for children with SAM is recommended

9.5 Treatment outcome

The mortality rate observed in this study is higher than SPHERE recommendation (mortality rate less than 10%) for inpatient management of SAM [24]. It also fell short of WHO suggestions of less than 5% [1]. Similarly, in comparison to other studies done in Sub-Saharan Africa, the mortality rate in this study is higher. The risk of mortality in Nutritional Rehabilitation Unit (NRU) for HIV-positive children in Sub-Saharan Africa was found to be 33.6% (range: 29.4-38.4) [1]. In a study done by Maitland K et al., mortality rate was reduced from 30% to 19% following a stricter application of WHO therapeutic guidelines [2]. However, the mortality rate in UTH malnutrition ward had persistently been above 30% [21] despite efforts made to adhere to the WHO treatment recommendations. Similar high mortality rate was observed in inpatient units in Malawi [16], indicating a possibility of regional variation in case presentation and response to treatment.

The fact that 34.8% of the children died within 48 hours of admission, with 65% being dead within a week's time, raises a concern. During the first 24 to 48 hours, children with severe malnutrition are at risk of hypoglycaemia, hypothermia and shock; and these conditions could have contributed to the high early mortality. Moreover the risk of the above complications is increased by the presence of bacteraemia. This is the critical period in inpatient management of children with SAM [4].

For a 59 bed capacity, the ward has more children than it can accommodate year round. The congestion of the ward, with more than one child per cot in need of treatment, makes management of the children difficult. Such a full ward coupled with the presence of children's caretakers and their accompanying siblings have made management even more challenging. This situation markedly increases the risk of bacteraemia via cross contamination and nosocomial infectons.Treatment outcomes are greatly compromised by the above listed factors. Since the advent of Community-based Therapeutic Programs (CTC), the case fatality of children with SAM has been reduced to less than 5% [26, 27]. More efforts need to be made to identify children suffering from SAM at an earlier stage through strengthening active case finding at the community level. In addition, the value of a supplementary feeding program which is lacking from the current CTC program in Lusaka needs to be looked into [28].

The effect of diarrhea on admission on outcome of the children also calls for improved community level interventions. In this case, the value of Zinc supplementation, oral rehydration solutions and water and sanitary interventions deserve a critical look [29].

9.6 HIV infection and survival of SAM children

The HIV prevalence found in this study stands higher than the 29.2% prevalence found in a recent meta-analysis done in Sub-Sahara Africa [25]. Moreover, it was found that HIV-positive children had higher risk of death than HIV-negative children, 48.3% vs. 35.5% (P=0.01). The increased risk of mortality was regardless of blood culture, admission diarrhea, sex, nutritional status and age. Although the background mortality (in HIV-negative children) in the ward is quite high, the increased risk of mortality in HIV-positive children, independent of other exposure factors raises a concern. The value of concomitant Antiretroviral (ARV) for children with SAM admitted to inpatient units is not known [8]. Due to underlying medical condition of HIV-positive children with severe malnutrition, there is consensus to first stabilize the children before starting them on ARV. The lag time to DNA PCR result for children less than 18 months, and pre-HAART baseline assessment would also have meant that a week would pass before ARVs are started. In such a circumstance, a viable and potentially effective strategy could be ensuring that HIV-positive children are closely followed up within the community (either through a growth monitoring program or healthy baby clinics) and diagnosis of malnutrition made at an earlier stage. This could enable starting nutritional treatment at an earlier stage; this has an advantage to save more lives.

HIV-positive children were found to stay longer than their HIV-negative counterparts at the time of death. Moreover, HIV-positive children were noted to initially respond to treatment before ultimately relapsing and succumbing to death. The effect of cross-infection as a cause of their relapse needs to be investigated.

10. LIMITATIONS

Cross infection after admission (to rule-out hospital acquired bacteremia) was not assessed in this study. This could be a major factor in negatively affecting treatment outcome as there is a high level of congestion and cot sharing in the ward due to high patient load. Other investigations such as stool and urine analysis could have added more value to our understanding of the cause of mortality. Investigations for Tuberculosis as a co-morbidity could have added a wealth of information. Besides, this analysis does not look into the quality of care provided during the period of admission. MUAC was not used as an admission criterion in the ward hence limiting the comparability of the study to more recent publication. The specific organisms in those children with mixed bacterial growth were not identified limiting our understanding of the prevalence of common organisms.

Analysis of presenting symptoms would have added more to the wealth of information but inconsistent data made it impossible.

11. CONCLUSION

The mortality rate of SAM children in the ward is unacceptably high. The prevalence of bacteremia and HIV is higher compared to other similar studies. Having bacteremia increased the odds of death by an almost two folds independent of HIV infection or admission nutritional status. Related to this, the relatively high resistance of the common organisms isolated to drugs under use in the unit calls for review. Use of Ciprofloxacin as a second line drug is recommended. Effort to strengthen the early case identification at community level should be made in order to prevent children from getting to the stage where they require a more intensive inpatient treatment.

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APPENDICES

APPENDIX 1

Enrolment and Follow up form

Part 1

1. Participants details

a. Date -----------------------------

b. Study Id number -----------------------------

c. Initials ------------------------------

d. Hospital number ------------------------------

e. Date of enrolment ----------------------------

f. Age of child ---------------- (DD/MM/YY) -------

g. Sex of child -----------------

h. Age of mother ------------------------------

i. Education standard of mother (a) Primary

(b) Secondary

(c) Tertiary

j. Occupation of mother ----------------------

2. Presenting signs and symptoms

a. Weight loss (-3 SD) --------------------------

b. Body swelling --------------------------------

c. Diarrhea and vomiting ----------------------

d. Cough ---

e. Fever --

f. Dermatosis -----------------------------------

g. Angular stomatitis --------------------------

h. HIV status

i. Others – specify

3. Use of antibiotics prior to presentation

a. Yes ---------- No ---------

b. Type

j. Amoxicillin ----------------------------

ii. Co-trimoxazole --------------------------

iii. Erythromycin -------------------------------

iv. Cephalosporin (specify) --------------------

v. Chloramphenical -----------------------------

vi. Others – (specify) ---------------------------

c. Duration --

4. Investigations done:

(i) Full blood count --------------------------

(ii) Blood m/c/s -----------------------------

Results of investigations

Final Diagnosis

Outcome.

APPENDIX 2

Consent Form 1

Invitation

You are invited to participate in this study that is looking at the bacteraemia and types of organisms isolated in severely malnourished children. It is being conducted by Dr Mwate Mwambazi-Mweene as part of fulfillment of Master of Medicine in Peadiatrics and Child Health. The study is being conducted in order to identify and precisely treat infections in these children.

Nature and purpose of the study

The study is being conducted in view of the fact that severely malnourished children are susceptible to infections. Knowledge of the common infecting organisms may help health care providers to treat children with severe malnutrition better.

Procedures of the study

If you agree to participate in the study, we will obtain information from you regarding age of child and social data. Samples of blood will be drawn and be transported to the laboratory for testing. The results of the tests will be communicated to you if you so wish.

Possible risks and discomforts

Your child will not be exposed to any added risks by enrolling into the study other than the usual risks faced when routinely collecting blood samples such as bleeding, infection and the discomfort of the needle prick.

Possible benefits

Apart from receiving treatment for his or her current infection, the recommendations generated from this study will contribute to the body of knowledge and many others. It may also help improve care of your child as more investigations will be done on him/her.

Confidentiality

All the information collected in this study is strictly confidential. Data that will be collected and reported will not include your name. Your child's name and personal details will not appear on the study files and therefore can not be traced to you.

Consent

Your participation in this study is purely voluntary. You and your child will not suffer any consequences if you decide not to participate in this study. You may also withdraw from the study at any time for any reason without consequences to you or your child's care.

Thank you for considering you and your child's participation into the study. If you have any questions, concerns and clarifications, please contact Dr Mwambazi-Mweene or The University of Zambia Research Ethics committee on the following addresses;

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APPENDIX 3

Consent Form 2

I, -- hereby confirm that I have been sufficiently explained to about the nature, conduct benefits and risks of this clinical study. I have also received, and/or read and understood the above written information about the study. I am aware that my personal details and that of my child will be anonymously processed into the research report. I have understood that I may voluntarily, at any point, withdraw my participation and that of my child from the study without suffering any consequences. I have been given sufficient time to ask questions and seek clarifications, and of own free will declare my participation and that of my child into the research study.

I have received a signed a copy of this agreement

Participant's signature or thumb print Date

Person obtaining informed consent Date