PREVALENCE AND SOME CAUSATIVE FACTORS
OF SEVERE ANAEMIA AMONG CHILDREN
ADMITTED TO THE ACUTE CARE UNIT
MULAGO HOSPITAL

BY

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PREVALENCE AND SOME CAUSATIVE FACTORS OF SEVERE ANAEMIA AMONG CHILDREN ADMITTED TO THE ACUTE CARE UNIT MULAGO HOSPITAL

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A Dissertation submitted in partial fulfillment of the requirements for the award of a Master of Medicine degree in Paediatrics and Child Health of Makerere University.

May 2003.
DECLARATION

I hereby declare that all the work presented in this dissertation is original unless otherwise acknowledged.

This work has not been presented to any other University for a degree award, nor has it been submitted elsewhere.

Signed

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DEDICATION

This dissertation is dedicated to my dear children Pauline, Daudi & Elizabeth;

and

to my dear husband Michael Ssenabulya, for their patience.
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(iii)
LIST OF ABBREVIATIONS AND ACRONYMS

ACU    Acute care unit  
CBC    Complete blood count  
CRP    C-reactive protein  
ESR    Erythrocyte Sedimentation rate  
G6PD   Glucose 6 phosphatase dehydrogenase  
Hb     Haemoglobin  
HbS    Sickle Cell haemoglobin  
HCT    Haematocrit  
HIV    Human immunodeficiency virus  
IDA    Iron deficiency anaemia  
MCH    Mean corpuscular haemoglobin  
MCHC   Mean corpuscular haemoglobin concentration  
MCV    Mean corpuscular volume  
MOH    Ministry of Health  
PCV    Packed cell volume  
RDW    Red cell distribution width  
SCA    Sickle Cell Anaemia  
SF     Serum ferritin  
TIBC   Total iron binding capacity  
WHO    World Health Organisation
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DEFINITION OF TERMS

Anaemia is a state in which the haemoglobin concentration has fallen below a threshold lying at two standard deviations below the median for a healthy population of the same age, sex, or stage of pregnancy.¹

Clinical presentation  The presenting symptoms and signs of severe anaemia
Severe anaemia       Haemoglobin level less than 5g/dl.
Type of anaemia      Level of haemoglobinisation and size of red blood cells.
Parasitaemia         The presence of any Plasmodium falciparum asexual forms on peripheral blood smears.
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ABSTRACT

Introduction

Anaemia is a major cause of childhood morbidity and mortality worldwide especially in developing countries. It is an important paediatric health problem in sub Saharan Africa where up to 45% of hospitalized children have severe anaemia and receive blood transfusion. Whereas severe anaemia is a common paediatric emergency in Mulago hospital in Uganda, its prevalence in children has not been established, and there is no up to date information on its aetiology.

Objective

To determine the prevalence and causative factors of severe anaemia among children admitted to the Acute Care Unit, Mulago Hospital.

Design

Cross sectional and case control study.

Setting

Mulago National Referral and Teaching Hospital, Kampala, Uganda

Participants

Children aged 3-60 months admitted to the Acute Care Unit from September 2002 to April 2003. Cases comprised of 92 children with a haemoglobin level less than 5g/dl. The controls comprised of 92 children with a haemoglobin level between 5g/dl to 11g/dl, matched with the cases for age and sex. Another 1400 children admitted to the Acute Care Unit from February to April 2003 were recruited for the prevalence study.

Measurements

Basic socio-demographic characteristics of the children and caretakers were collected using a questionnaire. A complete physical examination was performed and blood was taken for haemoglobin level, blood count, peripheral film, haemoglobin electrophoresis, C-reactive protein and serum ferritin. Stool was examined for hookworm ova and occult blood.
Statistical analysis
Data was processed using EPI-INFO and SPSS computer software packages, and summarized using frequency tables and histograms. The Chi-squared test was used for categorical variables and the students t-test for continuous variables. Multiple logistic regression was used to determine factors predictive of severe anaemia.

Results
Three hundred (21.4%) of the 1400 admitted children had severe anaemia. The majority (75%) of the severely anaemic children were less than 2 years of age. Most children with severe anaemia presented with fever (93.5%), difficulty in breathing (54.3%), heart failure (28.6%), and 20% had had previous blood transfusions. Koilonychia (OR 5.3, CI 1.46-19.0), gallop rhythm (OR 4.78, CI 1.83-12.97), splenomegaly (OR 3.68, CI 1.92-7.04), and hepatomegaly (OR 3.77, CI 1.92-7.04) were significantly associated with severe anaemia. However only koilonychia (OR 6.937, CI 0.03-0.52), gallop rhythm (OR 3.57, CI 1.34-9.34), a history of previous blood transfusion (OR 3.141, CI 1.143-10.53), and hepatomegaly (OR 3.471 CI 0.181-0.485) were independently associated with severe anaemia on logistic regression.
Malaria (58.7%), sickle cell gene (13%) and iron deficiency (13%) were the major causes of severe anaemia. The cause was not determined in 23.9% of children. Concerning the aetiology there was no statistically significant difference between the cases and controls. However iron deficiency anaemia was more common amongst the controls. There was no statistically significant difference in mortality between the cases and controls. Five of the cases had pneumonia and four were in heart failure.

Conclusions
The prevalence (21.4%) of severe anaemia amongst children admitted to the Acute Care Unit is unacceptably high. Malaria is still the leading cause of severe anaemia and one in five children had a history of previous blood transfusion.

Recommendations
There is need to reinforce measures for preventing malaria so as to reduce the frequency of severe anaemia in children.
There is need for a detailed prospective clinical audit of children admitted with severe anaemia in Mulago Hospital involving a higher number of children.
More studies are needed to determine the contribution of other causes such as HIV, folate and glucose 6-phosphate dehydrogenase enzyme deficiency to severe anaemia.
CHAPTER ONE

BACKGROUND INFORMATION AND LITERATURE REVIEW

1.0 INTRODUCTION

Anaemia is a recognized public health problem world wide affecting an estimated 30 percent of the world’s population. Most of the anaemic population lives in developing countries where high prevalence of anaemia is seen, particularly in young children, adolescents, women of childbearing age and pregnant women. It is among the six commonest causes of paediatric mortality in Uganda and the 5th commonest cause of death among children in Mulago hospital. Anaemia as a cause of childhood morbidity in Uganda and Africa in general has taken on new significance with the realization that blood transfusions commonly used to treat severe anaemia may be a major vehicle for HIV transmission. In Uganda 60% of the blood from the National blood bank is given to children which is high compared to other African countries where only 32.2% of the blood is used for transfusion of children. Severe anaemia is a common complication of diseases like malaria, an endemic disease. It can result from nutritional deficiencies like iron, and can be part of presentations of haemoglobinopathies like sickle cell anaemia, yet it can also worsen other preexisting conditions in children. Little is known about the relative contribution of malaria, helminthic infestations, iron deficiency and sickle cell disease to the aetiology of severe anaemia.

1.1 DEFINITION OF ANAEMIA

The World Health Organisation defines anaemia as a blood hemoglobin or haematocrit level or red cell mass below normal for age, sex, altitude and physiological state of the individual.

For children 6 months to 5 years anaemia has been defined as hemoglobin less than 11 g/dl and haematocrit less than 33%.

In this study, severe anaemia has been defined as hemoglobin level less than 5g/dl.
This definition has been derived from the paediatric guidelines for management of severe anaemia, in the Department of Paediatrics, Mulago hospital (Appendix V)

1.2 EPIDEMIOLOGY

A total of 2.17 billion people worldwide are anaemic by WHO criteria with a global prevalence rate of 30%. Asia and Africa are the most affected regions with prevalence rates of up to 50% in children and women while North America and Europe are the least affected with prevalence rates varying between 10% and 20%.

Within communities in the world, vulnerable groups in descending order of prevalence rates of anaemia are, pregnant women 51%, pre-school children 43%, low birth weight infants 30% to 40%, women and school children 30%, the elderly 10 – 20%, and adult men 5 – 15%.

In Brazil, Neuman found the prevalence of anaemia to increase with age up to 18 months old and then decreasing after. It was less prevalent in families where the father had a higher education level and where there was a higher total family income. In East Africa, the prevalence of anaemia ranged from 15-93% with a mean prevalence of 74%.

The Ministry of health reports anaemia as the tenth commonest cause of out patient morbidity accounting for 2.3% of the disease burden. In one study the prevalence of severe anaemia was 9% in children presenting to Acute Care Unit and various paediatric clinics.

In Uganda 64% of children are anaemic. Karaire found a prevalence of 62% of anaemia in apparently healthy children attending the young child clinic in Mulago hospital with a range of 3.9 gdl⁻¹ to 14.7 gdl⁻¹. Fifteen percent had severe anaemia. The most affected age group was 7-18 months.

1.3 CLINICAL FEATURES OF SEVERE ANAEMIA

The clinical presentation of a child with severe anaemia is variable and directly related to the pace at which the anaemia developed. If the anaemia worsened gradually
following chronic parasitaemia the child may have little or no symptoms and signs apart from pallor. If the fall in haemoglobin has occurred more rapidly, the child will present with signs of cardiac failure. Breathlessness on exertion occurs when haemoglobin is less than 4 g/dl. A significant proportion of patients of all ages with chronic iron deficiency anaemia demonstrate pica. There may be sub-optimal growth, irritability, yellow eyes, bone-pains and passing worms in stool.

**General Clinical Examination**

This may or may not reveal possible causes of severe anaemia. Pallor of the mucous membranes with jaundice may suggest a haemolytic anaemia, and marked pallor associated with petechiae or ecchymoses may suggest acute leukemia. The nails may become brittle and break easily or they may become concave (koilonychia) in shape in chronic iron deficiency. However koilonychia may also occur as an autosomal dominant trait, in haemochromatosis and in normal children during the first 2 years of life. Signs of chronic haemolytic anaemia like bossing of the head may occur.

**Cardiovascular System**

There is tachycardia, haemic murmur, gallop rhythm and pedal oedema. There may be a tender liver if there is congestive heart failure.

**Neuromuscular System**

Headache, vertigo, tinnitus, faintness, and lack of mental concentration, drowsiness, restlessness, and muscular weakness are common symptoms of severe anaemia.

**Gastrointestinal System**

Hepatomegaly which may be tender if heart failure is present. Splenomegaly may occur, and this worsens the anaemia by increasing haemolysis of the red blood cells.

**Respiratory System**

There may be tachypnoea, and there are fine basal crepitations if in congestive cardiac failure.
1.4 LABORATORY FINDINGS OF SEVERE ANAEMIA

These depend on the cause.

**Peripheral Film:** Malaria parasites may be seen on thick blood film. A thin blood film may show microcytosis and hypochromia in iron deficiency anaemia, thalassaemia, lead poisoning, sideroblastic anaemia, and anaemia of chronic diseases. A normocytic, normochromic picture may be seen in haemolytic anaemia, bone marrow failure, and acute blood loss. A macrocytic picture may be seen in vitamin B₁₂ or folate deficiency, and liver disease, but a dimorphic appearance may be seen if causes of both microcytosis and macrocytosis are present. Sickle cells, target cells, tear drop cells and Howell Jolly bodies may be seen in sickle cell anaemia.

In iron deficiency anaemia, the haematocrit is usually low with a reduced reticulocyte count. The mean cell haemoglobin concentration is usually less than 28% and mean cell volume is less than 80fl. Total iron binding capacity is usually high.

**Full blood count**

Mean cell volume is usually low and red cell distribution width is normal in heterogenous thalassaemia and chronic disease, whereas, mean cell volume is low and red cell distribution width is high in iron deficiency anemia and Sβ thalassaemia but both mean cell volume and red cell distribution width are high in folate and Vitamin B₁₂ deficiency.¹⁶ Pancytopenia with reticulocytosis may indicate hypersplenism, whereas pancytopenia with no reticulocytosis may indicate aplastic anaemia.

**Serum iron:** This is a measure of the amount of iron bound to transferrin and decreases in iron deficiency. During acute inflammatory conditions and infections, serum iron concentrations fall as iron is apparently redistributed to storage sites.

**Serum Transferrin Receptors (STFR):** Their concentration is pathologically increased in the presence of tissue iron deficiency and has been shown to be a sensitive indicator for this condition in adults. Most studies on STFR level in various conditions have been performed in adults. In children little is known about the clinical value of STFR.
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congenitions\textsuperscript{14} and they don't seem to have a role in the diagnosis of iron deficiency anaemia in young children exposed to malaria infection.\textsuperscript{16,17}

\textbf{Serum Ferritin}: Serum concentrations less than 12\(\mu g/l\) are considered diagnostic of tissue iron deficiency. However in the presence of inflammation (CRP 6mg/l) the cut off value is \(<100\mu g/l\textsuperscript{14,18,19}

\textbf{Bone Marrow}: It is unsuitable for routine use because it is invasive though it is the gold standard for measuring iron deficiency anaemia. However, some studies have found that a pathology report of absent bone marrow hemosiderin may be inaccurate in more than 30\% of cases and even when accurate may not necessarily signify the presence of iron deficiency anaemia. A measurement of serum ferritin level is recommended to confirm a clinical diagnosis.\textsuperscript{20}

\textbf{Stool}: Dark stool with positive occult blood and varying degrees of hookworm ova for those with hookworm infestation may be observed.

\textbf{Sickle Cell Anaemia}

The screening test for sickle cell is positive when the blood is deoxygenated. Haemoglobin electrophoresis is confirmatory for sickle cell disease, showing Haemoglobin SS.

\section*{1.5 CAUSES AND FACTORS ASSOCIATED WITH SEVERE ANAEMIA}

The common causes of severe anaemia seen in Mulago hospital were described by Vanier about forty years ago.\textsuperscript{58,22} Malaria and iron deficiency anaemia associated with heavy hookworm infections were found to be the commonest causes. Sickle cell anaemia was the third commonest cause.

Bakaki found the major causative factors of anaemia in the community to be malaria 58\%, chronic malnutrition 52\%, iron deficiency 18\%, and folate deficiency 13\%.\textsuperscript{23} Less common causes of severe anaemia include leukaemia, aplastic anaemia, acute haemorrhage, autoimmune haemolysis, glucose 6 phosphate deficiency and chronic...
renal disease. In a study done in Uganda, 100% of HIV infected children became anaemic between 9 and 36 months of age. Other studies have also brought out the role of HIV in causation of anaemia in children. In infants Ebrahim found the maximum number of admissions with severe anaemia occurred between ages of 3 and 9 months in Tanzania.

Children 6 months to 15 months are more at risk and a low socioeconomic status as well as a low level of the parents' education were found to be more in anaemic children. Infants born to mothers who are deficient in iron and pre-term babies have low iron stores, and are likely to get iron deficiency anaemia during infancy, or those on a prolonged milk diet because milk is a poor source of iron. Infants on fresh whole cow's milk lose serum protein and red blood cells in the gut due to altered integrity of the bowel mucosa.

Iron deficiency anaemia is very common in young children because of low content of bioavailable iron in the diet, increased loss due to repeated infection and infestation and high iron requirement for rapid growth.

1.5.1 Malaria and anaemia

Malaria is thought to be the primary cause of severe anaemia in at least 50% of subjects living in malaria-endemic areas. The disease is stable in approximately 95% of Uganda and over 90% of infections are due to Plasmodium falciparum. Plasmodium falciparum infection contributes to the aetiology and severity of anaemia through several mechanisms. These include direct destruction of parasitized red blood cells, immune mechanisms (including the destruction of unparasitized red cells) and dyserythropoiesis. Malaria may also contribute to iron deficiency by reducing iron absorption during acute episodes and through sequestration of iron in malaria pigment, and haemoglobinuria.

The role of malaria in the aetiology of anaemia is supported by the observations that in malaria – endemic areas, the incidence and age pattern of severe anaemia are strongly dependent on the intensity of Plasmodium falciparum transmission. Transmission is largely perennial with increases during the rainy season. Severe anaemia is a common complication in children with malaria. A recent study in Tanzania confirmed the role of
malaria as the largest contributor to the aetiology of severe anaemia in infants in highly endemic areas, accounting for about 60% of all cases compared with iron deficiency which accounted for about 30% of severe anaemia episodes. In the same study it was found that the groups that received malaria prophylaxis had lower frequencies of both severe anaemia and malaria.\textsuperscript{33}

In Kenya\textsuperscript{34} another study showed that Plasmodium falciparum infection was associated with reduced haemoglobin concentration in children and was the primary cause of severe anaemia in 46% children admitted to hospital. The mortality rate in children with severe malarial anaemia was 8.6% compared with 3.6% in children with severe anaemia due to other causes\textsuperscript{34}.

In a study in Senegal, severe anaemia was present in 73.1% and 52.1% of cases of severe malaria among children aged 0-3 years and 4-7 years respectively. Among young children, severe anaemia was associated with brief hyperparasitaemia or with prolonged lower parasitaemia. Older children have a lower risk of severe anaemia\textsuperscript{35}. In Papua New Guinea severe anaemia constituted 22% children with malaria, while in Malawi malaria associated severe anaemia accounted for 54% of malaria related deaths at one district hospital\textsuperscript{36, 37}. The prevalence of malaria associated severe anaemia was 8.5% among admissions in the same hospital.

The mean age of children presenting with severe malaria anaemia is about 1.8 years\textsuperscript{34}. The degree of anaemia is related to the infecting organism with Plasmodium falciparum causing severe haemolysis and anaemia. Studies in Zaire showed that paediatric blood transfusions given primarily for the treatment of malaria associated anaemia account for an estimated 25% of paediatric HIV infections.\textsuperscript{5}

\subsection{1.5.2 Iron deficiency anaemia}

Iron deficiency anaemia is the commonest micronutrient deficiency in the world. It contributes to low-birth weight, lowered resistance to infection and poor cognitive development. The WHO (1959) study group defined iron deficiency anaemia as "an anaemia brought about primarily by deficiency of iron in the body and characterized by progression from a normocytic blood picture to one that is microcytic hypochromic and responds to treatment with iron."\textsuperscript{39}
Due to the relatively low iron stores in children, iron deficiency is common around the time of growth spurt especially between the ages of 6 and 24 months, particularly if the initial birth weight is low.\textsuperscript{40}

Infants are born with iron stores in haemoglobin (75%) and in the tissues. Some studies have shown that children with iron deficiency are more likely to develop severe malarial anaemia\textsuperscript{41,42} and that iron supplementation in these children may significantly improve their haematological status\textsuperscript{33,43}. However, there are concerns that iron supplementation provides the developing parasites with the iron they require to develop\textsuperscript{44} and thus may worsen the severity of malaria and increase the frequency of malaria attacks.\textsuperscript{45,46}

\textbf{Sources of iron}

Grain products are the principle source of dietary iron followed by meat, poultry, fish, vegetables, legumes, nuts and soy. Animal products especially red meat contain the haeme iron that is readily absorbed, while plant products contain non-haeme iron that is not easily absorbed due to the presence of substances such as phytates and tannins that inhibit absorption.

\textbf{Iron bio-availability}

The absorption and utilization of iron depends on the balance between presence of substances that inhibit iron absorption and those that enhance iron absorption in a meal. Some food preparation methods such as fermentation, germination and soaking have the advantage of reducing phytate inhibitors and have been shown to improve iron bioavailability.

\textbf{1.5.3 Hookworm anaemia}

Intestinal helminths affect over one quarter of the world's population at any one time. Hookworms, which affect approximately 20% of the world's population, have the most significant effect\textsuperscript{27}. It is estimated that Ancylostoma duodenale sucks 0.15ml of blood per worm per day, while Necator Americanus sucks 0.03 - 0.05ml of blood per worm per day.\textsuperscript{47}
Prevalence and Causes of severe anaemia in admitted children

The prevalence of hookworm infestation increases with age in children. The amount of blood lost from the gut determines the development of anaemia. The severity of this anaemia depends upon worm load, the type of worm, the age of the child, and the nutritional status of the child including dietary iron intake. Up to 100mls of blood may be lost daily in heavy infestations. Children on an adequate iron intake may keep pace with blood loss so that anaemia does not develop. Among the geo-helminths only hookworm is associated with severe anaemia.

1.5.4 Sickle Cell Disease

About 1-2% of infants are born with sickle cell disease and anaemia is one of the earliest presentations of sickle cell disease in children. It is the most frequent hereditary haemolytic anaemia in Uganda and carries high morbidity and mortality. It is estimated that about 20% of the African population in Uganda are carriers of the sickle cell gene. In Mulago hospital sickle cell anaemia contributes to 14% of paediatric admissions and 10% mortality and most patients present with various manifestations of the disease such as anaemia, painful crisis, malaria, splenic sequestration crisis, aplastic crisis and hyperhaemolytic crisis.
CHAPTER TWO

2.0 PROBLEM STATEMENT

Anaemia is a global problem. It is widespread in developing countries especially the tropics. Countries with more than 10% anaemia prevalence in one or more of the vulnerable groups should consider anaemia as a significant public health problem requiring priority attention. Estimated prevalence rates of anaemia in children under 5 years are 56% in South Asia and Africa, 20% in East Asia, 14% in Europe and 8% in North America.²

Severe anaemia and malaria are also a significant burden on health facilities in sub-Saharan Africa, accounting for much of the hospitalization and use of external health services. In 1990, of 2433 children admitted to a Kenyan hospital, 29% had severe anaemia (Hb < 5 g/dl) and 18% of the severely anaemic children died.³³

In the 2001 Uganda Demographic Health survey, 64% of children were found to be anaemic and 7% had severe anaemia.² Available data from health units indicate that anaemia is one of the top ten health conditions that contribute to morbidity and mortality in children.⁴ In children it is the sixth commonest cause of mortality contributing to 6% of paediatric deaths.⁴ Mortality records in the Acute Care Unit for the months of December 2001 to February 2002 show severe anaemia to contribute 36.7%, 35.8%, and 42% of deaths respectively.⁵²

Severe anaemia is one of the commonest paediatric emergencies in Mulago hospital. In studies involving children with cerebral malaria, severe anaemia accounted for 7.2% - 20% of the cases.⁵⁵, ⁵⁶

Anaemia has implications for social and economic development including increased susceptibility to infection, impaired cognitive development and learning performance in children, thus lowering the effectiveness of investments in education.⁵⁷ It causes impaired physical growth and permanent adverse effects on neural functions and it compounds morbid conditions such as cardiac disease, pneumonia, and malnutrition.
Severe anaemia requiring transfusion is a challenge to health facilities in areas like Uganda where HIV infection is prevalent. Blood transfusion may not only be a vehicle for HIV infection but it is also costly to the health system and the patient’s family.\textsuperscript{53}

The Mulago Hospital Acute Care Unit records show that a total of 5633 children were transfused in the year 2001, giving an average of 15 children per day\textsuperscript{52}. In Tanzania the total cost of severe anaemia case management was found to be $16.29 per severe anaemia episode in infants under 1 year of age\textsuperscript{53}. In Uganda the cost of preparing a safe unit of blood is estimated at 30 US dollars\textsuperscript{6}. This is in addition to the cost of haematinics and antihelmithic drugs as well as antimalarial drugs, which are usually part of treatment of these children.

2.1 JUSTIFICATION OF THE STUDY

It is recognized that anaemia contributes significantly to the burden of disease in Uganda especially in young children and pregnant mothers.

Severe anaemia in Uganda contributes significantly to high child mortality and morbidity. The causes of severe anaemia are considered to be multi-factorial. The current practice is to try and treat all these conditions but this may not be the most efficient or cost effective method. Yet some studies have shown iron supplementation to be associated with a greater degree of haemolysis due to malaria.\textsuperscript{46}

There are no recent studies of the aetiology of severe anaemia in Uganda. It is almost forty years ago since Vanier reviewed causes of severe anaemia in children admitted to Mulago hospital,\textsuperscript{58} hence there is a large information gap. There was need to establish the prevalence and causative factors of severe anaemia among children admitted to hospital.

Therefore this study sought to establish the current magnitude, pattern and the causes of severe anaemia in Ugandan children. It was hoped that it would provide data that might lead to cost effective guidelines to the management of severe anaemia; and shed more light on the relationship between clinical features and the severity of anaemia.
The study was designed to answer the following questions:

2.2 RESEARCH QUESTIONS

1. What is the prevalence of severe anaemia among children admitted to the Acute Care Unit, Mulago Hospital?
2. What are the causative factors of severe anaemia among children admitted to the Acute Care Unit, Mulago Hospital?
3. What are the clinical features and type of anaemia among children with severe anaemia admitted to the Acute Care Unit, Mulago Hospital?
4. What are the clinical causes of mortality among children admitted with severe anaemia to the Acute Care Unit, Mulago Hospital?

2.3 OBJECTIVES

2.3.1 General
To determine the prevalence and identify some causative factors of severe anaemia among children admitted to the Acute Care Unit, Mulago hospital.

2.3.2 Specific
1. To establish the prevalence of severe anaemia among children admitted to the Acute Care Unit, Mulago Hospital?
2. To identify some causative factors of severe anaemia among children admitted to the Acute Care Unit, Mulago Hospital?
3. To describe the clinical features and type of anaemia among children with severe anaemia admitted to the Acute Care Unit, Mulago Hospital?
4. To describe the clinical causes of mortality among children admitted with severe anaemia to the acute care unit.

2.4 RESEARCH HYPOTHESIS

Malaria is the major cause of severe anaemia among children admitted to the Acute Care Unit.
CHAPTER THREE

METHODOLOGY

3.0 DESIGN

Cross sectional and case control study.

3.1 STUDY SETTING

Hospital based study which was carried out in the Acute Care Unit of Mulago National Referral and Teaching Hospital, Kampala, Uganda. Mulago Hospital is 4 kilometers north of Kampala City centre.

The population included patients from Kampala and peri urban areas as well as referrals from surrounding hospitals and up country district hospitals. In the Acute Care Unit, all children are seen first by the triage nurse who sends emergency cases to the doctors immediately. There is a minimum of three doctors on duty at any one time.

Those who are very ill and require admission are admitted for a night and the following day they are transferred to other wards if they are still very ill. If they are better they are discharged and followed up as outpatients. The emergency cases are resuscitated from the same place, while mildly ill children are treated as outpatients. Emergency laboratory tests such as blood slide for malaria parasites and haemoglobin levels are done from here. The bed capacity is 40 but the number of admitted children may sometimes go up to 100 necessitating sharing of beds by some children.

3.2 POPULATION

Target population:

Children 3 months to 60 months in Uganda
Prevalence and Causes of severe anaemia in admitted children

This group has been chosen because it is the age group that is more affected by anaemia among children.²

Accessible population:
A child 3 months to 60 months admitted in Mulago hospital.

Study population:
A child 3 months to 60 months admitted to the Acute Care Unit during the study period.

Study Unit: A child who fulfils the inclusion and exclusion criteria

3.3 SAMPLE SIZE ESTIMATION

3.3.1 Sample size estimation for the prevalence study

The sample size was estimated at 1398 for the prevalence study using the formula developed by Kish L.⁵

\[ n = \frac{Z^2 P(1-P)}{D^2} \]

where:

- \( Z \): standard normal deviation at 95% confidence interval (1.96)
- \( P \): the estimated prevalence of severe anaemia in the population 9%¹¹
- \( Q \): 100% - P
- \( = 91\% \ (0.91) \)
- \( D \): the difference between the estimates we would get and true values in the population. It is the error being allowed for 1.5% (0.015)

\[ n = \frac{(1.96)^2 \times 0.09 \times 0.91}{0.015 \times 0.015} \]

\[ = 1398 \]
3.3.2 Sample size estimation for the case control study

This was estimated using Fleiss’ formula for case control studies.\(^6\)

\[
\begin{align*}
n & = \frac{2(Z_{\alpha} + Z_{\beta})^2 \cdot PQ}{(P_1 - P_0)^2} \\
\end{align*}
\]

where

- \(n\) = minimum sample size
- \(Z_{\alpha}\) = The standard normal percentage point corresponding to 95% confidence interval (1.96)
- \(Z_{\beta}\) = The standard normal percentage point corresponding to 80% power (0.842)
- \(P_1\) = Expected population of exposure (malaria)\(^6\) among children with severe anaemia, that is 65% (0.65).
- \(P_0\) = The proportion of children who have malaria without severe anaemia 42%.
- \(P = \frac{P_0 + P_1}{2} = 53.5\)
- \(Q = (100 - P) = 46.5\)
- \(n = 2(1.96 + 0.842)^2 \times 53.5 \times 46.5 = 74\)

3.4 SELECTION CRITERIA

3.4.1 Inclusion Criteria for Cases

1. Children aged 3 months to 60 months admitted to the acute care unit during the study period.
2. Children with a haemoglobin level less than 5 g/dl.
3. Children with signed informed consent from caretaker.
3.4.2 Inclusion Criteria for Controls

1. Children aged 3 months to 60 months admitted to the acute care unit during the study period.
2. Children with a haemoglobin level 5 g/dl to 11 g/dl.
3. Children with signed informed consent from caretaker.

3.5. SAMPLING PROCEDURE

Children 3 months to 60 months admitted to the Acute Care Unit had their haemoglobin concentration determined by a laboratory technician using cyanhaemoglobin method. All children with haemoglobin levels less than 5 g/dl were enrolled as cases until a sample size of 92 children was achieved. The cases were then matched for age and sex with children who had haemoglobin levels 5 to 11 g/dl.

For the prevalence study, all children aged 3 to 60 months admitted to the Acute Care Unit were consecutively enrolled and they had their haemoglobin levels determined using the haemocue method until a sample size of 1400 children was achieved.

3.6 MEASUREMENTS

The following measurements were taken in all children recruited for the case control study:

i. Body weight was taken to the nearest 100g using a 25kg Salter scale 9 Salter weight Tronix, Birmingham, UK.

ii. Length / height was measured to the nearest millimeter using a stadiometer (length Board) manufactured locally according to a model provided by the Appropriate Resources Technology Action Group, London.

iii. Axillary temperature was taken using a digital Phillips thermometer, Amsterdam.

iv. Respiratory rate and heart rate were taken in one minute.
3.6.1 Data Collection Techniques

Children 3 months to 60 months presenting to the acute care unit had their haemoglobin level determined. The principle investigator enrolled those eligible for the study. Consent was sought and when granted, the principle investigator carried out a detailed history and clinical examination using a pretested and pre-coded questionnaire. *(Appendix II)*

The variables measured were from clinical history, clinical examinations and investigations.

A history including socio demographic characteristics, presenting complaints, birth weight, previous drug treatment, a history of bleeding, pica, history of previous blood transfusions, history of bleeding or jaundice in early neonatal life were elicited for each participant.

A complete physical examination was carried out by the principle investigator to assess the state of nutrition of each participant, pallor of palms, tongue and mucous membranes, jaundice, hepatosplenomegaly and any external features of bleeding such as petechiae. Features of iron deficiency such as koilonychia were looked for and signs of congestive heart failure and respiratory distress recorded. Fever was defined as an axillary temperature of $\geq 37.5 \, ^{\circ}C$.

The spleen and liver were measured in the supine position in the mid-clavicular line. Congestive cardiac failure was defined as raised jugular venous pressure, or a tender liver or a gallop rhythm.

Respiratory distress was defined as chest in-drawing or flaring of alae nasi or use of accessory muscles of respiration.

Treatment and diagnosis on admission were also entered in the questionnaire. *(Appendix II)*
3.7 LABORATORY TESTS

3.7.1 Blood Collection

The principle investigator drew 4 milliliters of venous blood under aseptic conditions from all the cases and selected controls.

The skin was cleansed with 70% alcohol and a 5 milliliters sterile plastic disposable syringe with a 21-gauge needle was used to draw blood. A piece of sterile gauze was used to exert pressure at the puncture site to stop further bleeding. The needle was then removed from the syringe and blood put into containers. This was done to minimize the haemolysis of cells that occurs on forcing the blood through the needle. Two milliliters of blood was put in clot activator specimen containers, and centrifuged. One milliliter of serum was put in cryovials and kept in a deep freezer for analysis of serum ferritin and C-reactive protein levels.

Two milliliters of the blood was put in sequestrine bottles for determination of total red blood cell count, mean cell volume, mean cell haemoglobin concentration, mean cell haemoglobin, reticulocyte count, packed cell volume, and haemoglobin electrophoresis. Thin and thick blood smear were done immediately. Specimens were taken to the laboratory for analysis within an hour of collection.

For the prevalence study, all children aged 3 months to 60 months admitted to the Acute Care Unit had haemoglobin levels done using a Haemocue photometer (Ångelholm, Sweden).

The child’s finger was cleaned with 70% alcohol solution and then pricked. A drop of blood was placed on the micro cuvettes, and excess blood wiped off leaving approximately 10µl, which is the capacity of the microcuvette. Haemoglobin levels were written in the child’s medical chart. Parents were informed when their child’s haemoglobin level was < 5 g/dl and standard treatment was initiated. (Appendix V)
3.7.2 Haemoglobin electrophoresis

This was done on a filter paper 3 mm on the strand – Electrophoresis tank. The cells were washed four times using normal saline at a revolution of 2500r/min for 5 minutes to wash off other proteins which might interfere with the haemoglobin bands. Then two drops of distilled water were added to lyse the red blood cells. 1ml of chloroform was added and the sample was spinned to separate the haemolysate from the debris. A strip was then cut to the size of the tank. It was folded into two equal parts and then labeled with sample numbers and controls. It was soaked in a tris buffer and barbitone buffer at a ratio of 1:4. Blotting was then done to remove excess buffer solution. The strip was suspended on the wire of the electrophoresis tank so that one end touched the barbitone buffer (pH 8.6) at the anode and the other end touched the barbitone buffer at the cathode. Drops of the samples and the controls were then seeded at the labeled points of the strip and the tank was then covered and connected to a direct current with a voltage of 200 volts. The strips were read after 16 hours by comparing with the controls on the same strips. Other haemoglobinopathies such as thalassaemia were not investigated for because of lack of facilities.

3.7.3 Films

These were done using new slides. A drop of blood was put in the centre of the slide and a film made. At least 3 films were prepared and the best chosen and stained with Giemsa stain. Thin smears were examined for erythrocyte morphology and malaria species. Thick films were also made to look for haemoparasites. Giemsa Stain (2%) was used. Malaria parasites were counted against 200 leucocytes. If less than 10 parasites were seen, the counting was continued up to 500 leucocytes. The parasitaemia /μl was calculated using the formula: 62

\[
\text{Parasitaemia} / \mu l = \frac{\text{Number of parasites} \times \text{WBC count (8000)}}{\text{Number of WBC counted (200)}}
\]

Malaria species were identified from the thin smear.

A 10% sub sample of slides was re-read at random by a laboratory technologist and haematologist. Results were recorded on the laboratory form (Appendix III)
3.7.4 Stool Specimen

After collecting blood specimens, a stool examination container was given to the attendant to fill one third of it with the child’s stool. Macroscopically the stool was examined for blood, and microscopically for ova, cysts and red blood cells.

Stool was examined for parasites by mixing the stool with two drops of normal saline on one of the glass slides mounted with a cover slip and examined with a light microscope and x 40 objective lens was used.

Infestation was classified as light, moderate and heavy according to the WHO criteria. Light if there are 1 – 1999 eggs per gram (epg), moderate if there are 2000 – 4999 epg, and heavy if there are ≥ 5000 epg.

Hookworm counts were obtained for all study subjects and recorded. Other parasites present were also reported for patient care. Occult blood test was done using haematocult test method. Color change was observed after 30 seconds. A positive reaction produces a blue color and no detectable blue color anywhere on the filter paper if the reaction is negative. Any other colour change other than blue was regarded as a negative reaction.

Occult blood screen was based on the haemoglobin-catalysed oxidation of phenolic compounds present in the guaiac to blue colored quinones.

When a faecal specimen containing occult blood is applied to the test paper, contact is made between haemoglobin and the guaiac. A pseudoperoxidase reaction occurs upon the addition of the developer, with a blue chromatogen forming.

3.7.5 Biochemistry

Samples in the clot activator container were centrifuged at 100x for 5min at room temperature and serum collected. Sera were then stored in cryovials at −20°C pending serum ferritin assays. Ferritin was measured by fluorescent linked immunoassay using an automated immunoassay analyser (IMX systems). The advantage of the immunoradiometric assay are its quantitative and reproducible results together with its increased sensitivity in detecting low iron stores as compared with the histochemical method. An estimation of stainable iron in the bone marrow although a traditional method for assessing body iron stores was not used in this study. It has the disadvantage
of being subjective, semi-quantitative and invasive. Some studies have also shown that
the absence of stainable bone marrow iron does not always indicate iron deficiency
anaemia.\textsuperscript{20} Similarly the serum sample for C-reactive protein was stored at \(-20^{\circ}\text{C}\) while
awaiting assay. C-reactive protein was determined using the C-reactive protein latex
test, in which C-reactive protein reagent contained latex particles, coated with human C-
reactive protein antibody mixed with serum. If the serum contained C-reactive protein at
a level greater than 6mg/l the particles agglutinated, constituting a positive test. For the
quantification of C-reactive protein, the sample was diluted over a range of dilutions and
each tested qualitatively. The C-reactive protein level was then estimated from the last
dilution with visible agglutination by multiplying the titre in the last dilution step with
the conversion factor specified on the kit to get the results in mg/l. A patient was
categorised as iron deficient if one of the following or any combination of them was
present. Serum ferritin less than 100 \(\mu\)g/l in the presence of inflammation (CRP more
than 6 mg/l), or serum ferritin less than 12 \(\mu\)g/l in the absence of inflammation (CRP
less than 6 mg/l.)\textsuperscript{14}

3.8 DATA ANALYSIS

Data obtained was coded and then entered using EPI-INFO 6.4 computer software
package. Analysis was done using SPSS 10.0, with assistance of a statistician.
Data was summarized using frequency tables, bar charts, and histograms.
The Chi-squared test for association between severe anaemia and categorical variables
and the student’s t-test for the association between severe anaemia and continuous
variables was used.

3.9 QUALITY CONTROL

The questionnaire was pre-tested before the commencement of the study. The research
assistant was trained by the principle investigator on how to take specimens from
patients. The principle investigator took the history, carried out physical examination
and filled in the questionnaire. The principle investigator and an experienced laboratory
technologist read the peripheral film reports. A senior independent haematologist
examined 10% of the slides chosen at random. Questionnaires were crosschecked by the principle investigator for completeness before leaving the acute care unit.

3.10 PERMISSION FOR STUDY AND ETHICAL CONSIDERATIONS

Consent to carry out the study was obtained from:

1. Department of Paediatrics and Child Health, Makerere University.
2. Makerere University Faculty of Medicine Research Committee.
3. Mulago Hospital Ethics committee.
4. The Uganda National Council for Science and Technology.

Written informed consent was sought from the parents or caretakers of the children before they participated in the study. The child’s personal identifiers were not used in the final analysis and will not be used in any publications of this research. At all times proper patient management took priority over the conduct of the study. Children found with life threatening severe anaemia were given emergency blood transfusion. Laboratory results were availed immediately to the ward doctors for appropriate management.
4.1 Description of the study subjects for the case control study

One hundred and eighty-four children were enrolled for the case control study. Fifty percent of these (92) had severe anaemia (Hb < 5 g/dl) and the other fifty percent (92) had non-severe anaemia (Hb 5-11 g/dl). In this study too, the majority of children were Baganda by tribe 120 (65%) and there were 50 males and 42 females with a male to female ratio of 1:1.2. The mean age was 19.7 months. The baseline characteristics of the children with severe anaemia and non-severe anaemia were similar as shown in Table 1.

Table 1. Baseline Characteristics of 184 children with severe anemia and non-severe anemia admitted to the Acute Care Unit Mulago Hospital from September 2002 to December 2002.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (54.3)</td>
<td>50 (54.3)</td>
<td>1.00</td>
<td>0.75-1.34</td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>42 (45.7)</td>
<td>42 (45.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Primary</td>
<td>62 (67.4)</td>
<td>63 (68.5)</td>
<td>0.950</td>
<td>0.72-1.33</td>
<td>0.870</td>
</tr>
<tr>
<td>≥ Secondary</td>
<td>30 (32.6)</td>
<td>29 (31.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father’s Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Primary</td>
<td>49 (53.3)</td>
<td>49 (53.3)</td>
<td>1.00</td>
<td>0.54-1.86</td>
<td>1.000</td>
</tr>
<tr>
<td>≥ Secondary</td>
<td>43 (46.7)</td>
<td>43 (46.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTHW1</td>
<td>46 (51.1)</td>
<td>46 (51.1)</td>
<td>-</td>
<td>-</td>
<td>0.956</td>
</tr>
<tr>
<td>Professional</td>
<td>7 (6.7)</td>
<td>6 (7.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other2</td>
<td>37 (41.1)</td>
<td>38 (42.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father’s Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Business</td>
<td>18 (24.1)</td>
<td>21 (24.1)</td>
<td>-</td>
<td>-</td>
<td>0.537</td>
</tr>
<tr>
<td>Professional</td>
<td>12 (13.3)</td>
<td>15 (17.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other2</td>
<td>60 (66.7)</td>
<td>51 (58.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Full Time House Wife
2 Unskilled labour
CI = Confidence Interval
OR = Odds Ratio
4.2 Description of the study subjects for the prevalence study

From February to April 2003, one thousand four hundred admitted children aged 3 to 60 months were studied to determine the prevalence of severe anaemia. There were 769 (54.9%) males and 631 (45.1%) females with a male: female ratio of 1:1.2. The mean age was 19.5 months and the median age was 14 months. The majority of children were Baganda by tribe 950 (67.8%). The rest were Banyankore 88 (6.2%), Basoga 61 (4.4%), Banyarwanda 37 (2.6%), others were more or less equally distributed among other tribes within Uganda.

4.3 The prevalence of severe anaemia amongst 1400 children admitted to the Acute Care Unit.

The prevalence of severe anaemia (Hb < 5 g/dl) amongst the 1400 children aged 3 months to 60 months admitted between February 2003 and April 2003 was 21.4% (300 children). The prevalence was highest between 13 and 36 months of age.
Prevalence and Causes of severe anaemia in admitted children

The children admitted with severe anaemia were: 115 of 628 children in the age group 3-12 months, 110 of 415 children in the age group 13-24 months, 43 of 177 children in the age group 25-36 months, 19 of 106 children in the age group 37-48 months and 13 of 74 children in the age group 49-60 months. Their prevalence is shown in figure 1 below.

Figure 1. Prevalence of severe anaemia within age groups amongst 1400 children admitted to the Acute Care Unit, Mulago Hospital, February-April, 2003
Prevalence and Causes of severe anaemia in admitted children

The majority of severely anaemic children were less than 24 months of age (75%). There is a marked reduction in numbers of children with severe anaemia thereafter as shown in figure 2.

Figure 2. Distribution of 300 severely anaemic children, by age group, Acute Care Unit, Mulago Hospital February – April 2003
4.4 Causes of severe anaemia amongst children admitted to the Acute Care Unit

The leading cause of severe anaemia was malaria accounting for 54 (58.7%) of the 92 cases, followed by sickle cell anaemia with 12 (13%), and iron deficiency with 12 (13%) of the cases. Among the 92 controls the leading causes of anaemia were malaria accounting for 44 (47.8%), iron deficiency with 23 (25%) followed by sickle cell anaemia with 6 (6.5%) as shown in figure 3. Amongst the causes there was no statistically significant difference between the cases and controls.

Figure 3. Causes of anaemia amongst children (aged 3-60 months) admitted to Acute Care Unit, Mulago Hospital

SCA  Sickle Cell Anaemia
ID  Iron Deficiency Anaemia (Ferritin parameter used)
Prevalence and Causes of severe anaemia in admitted children

N.B. some children had more than one cause of anaemia, hence the numbers may not add up to 100%.

Although iron deficiency was more common amongst the controls as compared to the cases, the difference was not statistically significant (OR=0.494; 95% CI=0.233-1.048; p=0.063). Of the children with severe anaemia only one child had hookworm ova, compared to 2 children among the controls. The mean malaria parasite density was higher in the cases than in the control study group with values of 53,675.03 and 101,177.59 respectively.

Other causes of severe anaemia

Twenty-two (23.9%) of the 92 children with severe anaemia could not be categorized among the commonest causes but had diverse causes as shown in table 2.

Table 2. Other causes of severe anaemia among children admitted to the Acute Care Unit, Mulago Hospital

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysentery</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobinuria</td>
<td>2</td>
</tr>
<tr>
<td>Folate deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>2</td>
</tr>
<tr>
<td>Hypochromia and microcytosis (with normal ferritin levels)</td>
<td>4</td>
</tr>
<tr>
<td>Kwashiorkor with macrocytosis</td>
<td>1</td>
</tr>
<tr>
<td>Unknown cause with a reticulocytosis</td>
<td>2</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
</tr>
</tbody>
</table>

§ Based on clinical suspicion
Prevalence and Causes of severe anaemia in admitted children

Amongst the controls, there were 25 patients whose cause of anemia could not be categorized among the commonest causes. However 1 had dysentery and another had septicemia. The cause of anemia in the remaining 22 patients could not be established.

Multiple causes of severe anaemia

In the group of children with severe anaemia, 3 (3.2%) children had malaria and iron deficiency, 4 (4.3%) children had both malaria and sickle cell anaemia and 1 (1.1%) child had both iron deficiency and sickle cell. None of the children had all the three conditions. In the group of children with non-severe anaemia 4 (4.3%) children had malaria and iron deficiency, 2 (2.2%) children had both malaria and sickle cell anaemia and none of children had both iron deficiency and sickle cell anaemia. None of the children had all the three conditions.
4.5 Clinical features of children with severe anaemia and non-severe anaemia admitted to the Acute Care Unit, Mulago Hospital.

4.5.1 Findings in the history

A history of difficulty in breathing was significantly more common amongst the controls whereas previous transfusions, previous admissions and a history of easy fatigability were more common among the cases. The mean duration of fever was 6.07 and 5.78 days in the cases and controls respectively (p value 0.765). The miscellaneous complaints included cough in 27 children and enlarged spleen in 3 children as shown in table 3 below.

Table 3. Findings in the history of children with severe anaemia and non-severe anaemia

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Fever</td>
<td>86 (93.5)</td>
<td>80 (87.9)</td>
<td>1.971</td>
<td>0.696 - 5.577</td>
<td>0.195</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>50 (54.3)</td>
<td>63 (68.5)</td>
<td>0.548</td>
<td>0.300 - 1.000</td>
<td>0.049*</td>
</tr>
<tr>
<td>Convulsions</td>
<td>29 (31.5)</td>
<td>35 (38.5)</td>
<td>0.737</td>
<td>0.400 - 1.355</td>
<td>0.325</td>
</tr>
<tr>
<td>Easy fatigability</td>
<td>13 (14.6)</td>
<td>5 (5.7)</td>
<td>2.839</td>
<td>0.967 - 8.339</td>
<td>0.050</td>
</tr>
<tr>
<td>Yellow eyes</td>
<td>27 (29.3)</td>
<td>24 (26.1)</td>
<td>1.177</td>
<td>0.617 - 2.247</td>
<td>0.621</td>
</tr>
<tr>
<td>Red / Tea color urine</td>
<td>8 (8.7)</td>
<td>5 (5.4)</td>
<td>1.657</td>
<td>0.521 - 5.270</td>
<td>0.388</td>
</tr>
<tr>
<td>Pica</td>
<td>16 (17.8)</td>
<td>17 (18.7)</td>
<td>0.941</td>
<td>0.442 - 2.002</td>
<td>0.875</td>
</tr>
<tr>
<td>Previous blood transfusion</td>
<td>19 (20.7)</td>
<td>7 (7.9)</td>
<td>3.049</td>
<td>1.212 - 7.667</td>
<td>0.014*</td>
</tr>
<tr>
<td>Previous admission</td>
<td>39 (42.4)</td>
<td>23 (25.8)</td>
<td>2.112</td>
<td>1.125 - 3.963</td>
<td>0.019*</td>
</tr>
</tbody>
</table>

* Statistically significant difference between cases and controls p < 0.05

n = Number of children
4.5.2 Physical signs of children admitted with severe and non-severe anaemia.

Koilonychia, gallop rhythm and hepatosplenomegaly were strongly significantly associated with severe anaemia.

Table 4. Physical signs of children with severe and non-severe anaemia

<table>
<thead>
<tr>
<th>Signs</th>
<th>Cases n (%)</th>
<th>Controls n (%)</th>
<th>OR</th>
<th>CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wasted (-2SD)</td>
<td>11 (12.0)</td>
<td>14 (15.2)</td>
<td>0.757</td>
<td>0.324 – 1.768</td>
<td>0.519</td>
</tr>
<tr>
<td>Stunted (-2SD)</td>
<td>30 (32.6)</td>
<td>24 (26.1)</td>
<td>1.371</td>
<td>0.725 – 2.594</td>
<td>0.331</td>
</tr>
<tr>
<td>Severe pallor</td>
<td>69 (75)</td>
<td>28 (30.4)</td>
<td>2.69</td>
<td>1.85 – 3.91</td>
<td>0.000*</td>
</tr>
<tr>
<td>Koilonychia/brittle nails</td>
<td>14 (15.2)</td>
<td>3 (3.3)</td>
<td>5.265</td>
<td>1.459 – 19.006</td>
<td>0.009%</td>
</tr>
<tr>
<td>Bone tenderness</td>
<td>4 (4.4)</td>
<td>1 (1.1)</td>
<td>4.184</td>
<td>0.459 – 38.175</td>
<td>0.211%</td>
</tr>
<tr>
<td>Pedal Oedema</td>
<td>10 (11.1)</td>
<td>5 (5.4)</td>
<td>2.175</td>
<td>0.713 – 6.637</td>
<td>0.164</td>
</tr>
<tr>
<td>JVP raised</td>
<td>2 (2.9)</td>
<td>1 (1.5)</td>
<td>1.971</td>
<td>0.175 – 22.251</td>
<td>1.000%</td>
</tr>
<tr>
<td>Gallop rhythm</td>
<td>26 (28.6)</td>
<td>7 (7.6)</td>
<td>4.78</td>
<td>1.83 – 12.97</td>
<td>0.0005*</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>73 (60.8)</td>
<td>19 (29.7)</td>
<td>3.679</td>
<td>1.921 – 7.043</td>
<td>0.000*</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>73 (60.8)</td>
<td>19 (29.7)</td>
<td>3.679</td>
<td>1.921 – 7.043</td>
<td>0.000*</td>
</tr>
<tr>
<td>Tender liver</td>
<td>14 (18.9)</td>
<td>3 (4.2)</td>
<td>5.367</td>
<td>1.471 – 19.575</td>
<td>0.008%</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>14 (15.7)</td>
<td>17 (18.5)</td>
<td>0.891</td>
<td>0.587 – 1.355</td>
<td>0.577</td>
</tr>
</tbody>
</table>

* Fisher's exact test

* Statistically significant difference between cases and controls (P < 0.05)

n = Number of children
4.5.3 Logistic regression for predicting severity of anaemia

Since the clinical factors associated with severe anaemia might themselves be affecting each other, logistic regression was carried out to establish which factors were independently associated with severe anaemia as shown in table 3.

Table 5. Logistic regression for predicting severity of anaemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous transfusion</td>
<td>3.141</td>
<td>1.143 – 10.531</td>
<td>0.026*</td>
</tr>
<tr>
<td>Previous admission</td>
<td>1.526</td>
<td>0.282 – 1.523</td>
<td>0.326</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>6.937</td>
<td>0.030 – 0.518</td>
<td>0.006*</td>
</tr>
<tr>
<td>Gallop rhythm</td>
<td>3.568</td>
<td>1.363 – 9.341</td>
<td>0.009*</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>2.053</td>
<td>0.208 – 1.266</td>
<td>0.117</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>3.471</td>
<td>0.181 – 0.485</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*p value significant at < 0.05

Koilonychia, gallop rhythm, previous transfusion, and hepatomegaly were significantly associated with severe anaemia.
4.6 Type of anaemia in children with severe and non-severe anaemia

A hypochromic microcytic picture was significantly more common among the children with non-severe anaemia (Hb > 5g/dl) where as macrocytosis was significantly more common among the group with severe anaemia as shown in Table 4.

<table>
<thead>
<tr>
<th>Type of anaemia</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normocytic</td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normochromic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>10 (10.9)</td>
<td>11 (12.0)</td>
<td>0.90</td>
<td>0.33-2.43</td>
<td>1.000</td>
</tr>
<tr>
<td>No (%)</td>
<td>82 (89.1)</td>
<td>81 (88.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypochromic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microcytic</td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>25 (27.2)</td>
<td>39 (42.4)</td>
<td>0.51</td>
<td>0.26-0.98</td>
<td>0.044*</td>
</tr>
<tr>
<td>No (%)</td>
<td>67 (72.8)</td>
<td>53 (57.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrocytic</td>
<td>n(%)</td>
<td>n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>17 (18.5)</td>
<td>3 (3.3)</td>
<td>7.76</td>
<td>2.02-34.85</td>
<td>0.00075*</td>
</tr>
<tr>
<td>No (%)</td>
<td>65 (81.5)</td>
<td>89 (96.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR = Odds ratio
CI = confidence intervals
1 Coulter counter values used.
2 MCV < 80 & MCHC < 30
3 MCV > 100
n=Number of cases

There was a group of 52 children among the severely anaemic and 24 among the control group, who had a dimorphic picture (with macrocytes and microcytes), by peripheral film.

Children with both a hypochromic microcytic picture and iron deficiency anaemia (Ferritin parameter) among the cases and controls were 6 and 18 respectively.
4.7 Causes of mortality among children with severe anaemia.

Seven children with severe anaemia died and another 5 children with non-severe anaemia died. The case fatality rate was 7.6% amongst the cases and 5.4% among controls.

Amongst the severely anaemic children 2 were reported to have died of severe bronchopneumonia, two had congestive heart failure one died from aspiration pneumonia, one had cerebral malaria and one child was suspected to have bacterial meningitis. All the dead children had malnutrition except one. One of the children had autopsy, which showed cerebral malaria.

Figure 4. Clinical diagnosis among children who died

![Bar Chart]

Number of Cases

- **Pneu**: Pneumonia
- **CM**: Cerebral malaria
- **Mening**: Meningitis
- **Other**: No clinical diagnosis established

Some children had more than one diagnosis hence the numbers may not add up to 7.
4.8 Haemoglobin electrophoresis

Twelve children (13%) amongst the cases and 6 (6.5%) among the controls had the sickle cell gene as shown in Figure 5 below.
4.9 Haematological profile

Mean malaria parasite density was higher among the controls than the cases. Mean serum ferritin and mean C-reactive protein values were higher amongst the cases as shown in Table 7 below.

Table 7 Haematological Profile

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (± SD)</td>
<td>Mean (± SD)</td>
</tr>
<tr>
<td>Malaria parasite density (μ/l)</td>
<td>53657.03 (113,516.6)</td>
<td>101,177.59 (248,702.6)</td>
</tr>
<tr>
<td>Serum Ferritin (μ/l)</td>
<td>457.8 (307.3)</td>
<td>369.8 (343.4)</td>
</tr>
<tr>
<td>C-Reactive Protein (mg/dl)</td>
<td>44.5 (46.9)</td>
<td>39.6 (32.7)</td>
</tr>
</tbody>
</table>

4.10 Serum ferritin profile

Serum ferritin levels were lowest in children amongst the controls as shown in Figure 6 below.

Fig. 6 Frequencies of Serum Ferritin Levels

![Bar chart showing frequencies of serum ferritin levels in cases and controls. The chart indicates lower levels in severe anaemia cases compared to non-severe anaemia cases.](chart.png)
4.11 C-Reactive Protein Profile

C-Reactive Protein levels of more than 6mg/dl indicated inflammation. 11 children amongst the controls and 3 children amongst the cases had no inflammation according to CRP levels as shown in Table 8 below.

Table 8  C-Reactive Protein Profile

<table>
<thead>
<tr>
<th>CRP level mg/dl</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>3 (3.3)</td>
<td>11 (8.7)</td>
</tr>
<tr>
<td>12.00</td>
<td>17 (18.5)</td>
<td>10 (10.9)</td>
</tr>
<tr>
<td>24.00</td>
<td>32 (34.8)</td>
<td>32 (34.8)</td>
</tr>
<tr>
<td>48.00</td>
<td>21 (22.8)</td>
<td>25 (27.2)</td>
</tr>
<tr>
<td>96.00</td>
<td>18 (19.6)</td>
<td>13 (14.1)</td>
</tr>
<tr>
<td>192</td>
<td>00 (0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>384</td>
<td>1 (1.1)</td>
<td>00 (0)</td>
</tr>
</tbody>
</table>

4.12 Stool analysis

The test for Occult blood was positive in 5 (5.4%) of the cases and 13 (14.1%) of the controls. Hookworm ova with a total worm load of 840 ova/gm of stool was found in 1 child with severe anaemia and two children with non-severe anaemia were found to have hookworm ova. Other parasites found in the stool included Giardia lamblia, trichuris tricuria, entamoeba coli and ascaris lumbricoides.
CHAPTER FIVE

DISCUSSION

This study was designed to determine the prevalence of severe anaemia amongst children aged 3 to 60 months admitted to the Acute Care Unit of Mulago Hospital and to determine some causative factors, clinical features, type of anaemia as well as the clinical causes of mortality.

5.1 Prevalence of severe anaemia

The prevalence of severe anaemia was 21.4% which is much higher than in two previous studies done in Mulago Hospital where the prevalence was found to be 9% and 10.4% respectively\textsuperscript{11,56}. It is also higher than the 7% reported in the 2001 Uganda health demographic survey\textsuperscript{12}. The higher prevalence can be explained by the fact that the present study was looking at a highly selected group of children who were admitted in hospital and who were all ill, whereas the other studies included children who were well. Secondly the age group in the present study was limited to children between 3 months and 60 months who are known to be most affected by severe anaemia\textsuperscript{2} whereas in the above studies the age group was much wider including older children who are less affected by severe anaemia.

The prevalence of 21.4\% in this study is also higher than that in some West African studies such as in Ibadan Nigeria\textsuperscript{65} and in Accra Ghana\textsuperscript{7} where prevalence was reported as 5.9\% and 14\%, respectively. This can be explained by the fact that the Nigerian study was retrospective. This means that the medical personnel may have missed some severely anaemic children.

The majority of the severely anaemic children in the current study were less than 24 months of age (75\%) and there is a marked decline in numbers of children with severe anaemia thereafter. This could be due to improved immunity towards malaria leading to fewer episodes and also to less severe forms of malaria.
5.2 Causative factors among children admitted with severe anaemia.

5.2.1 Malaria

Malaria was the main causative factor and contributed to 58.7% of the 92 children with severe anaemia and 47.8% of the 92 children with non-severe anaemia. The difference between the two groups of children was, however, not statistically significant (OR 1.55 CI 0.83-2.9).

While there may be several causes for anaemia, *Plasmodium falciparum* contributes to the aetiology of severe anaemia by direct destruction of parasitized red blood cells. It also causes anaemia through immune mechanisms that destroy both parasitized and non-parasitized red cells, or suppression of the bone marrow as a result of the infection. Malaria being the leading cause of anaemia is not surprising since the disease contributes to 20% of all hospital admissions.

Secondly the study was carried out during the rainy months where transmission of malaria is high. In epidemiological studies, a strong correlation has been reported between the incidence of severe anaemia and the intensity of *Plasmodium falciparum* transmission. In addition, malaria control trials have been followed by marked improvements in haematological indices in children.

In the current study, the mean parasite density was surprisingly higher among the controls than the cases. This could be due to the fact that 61% of cases had been on antimalarial therapy compared to 50% among controls. It could also have resulted from sequestration of the parasites in the liver and other organs.

The predominance of malaria in this study is comparable to that in other studies done in Tanzania by Ebrahim and Menendez where malaria accounted for 57% and 60% of children with severe anaemia respectively. This was not surprising since the children in the present study were in a similar geographical area and in a malaria endemic region.
Prevalence and Causes of severe anaemia in admitted children

However the finding of severe anaemia secondary to malaria in the current study is still higher than that found earlier in Mulago Hospital, and Ibadan, Nigeria where malaria accounted for 38.5% and 46% of children respectively. In the Nigerian study however children less than 3 months of age were included yet malaria contributes little to the aetiology of severe anaemia in this age group. In the study done in Mulago Hospital the age range was wider and included older children aged 5 years to 12 years, who have acquired some immunity to malaria and are therefore less likely to present with severe malarial anaemia.

The other reason for the high prevalence of malaria in this study could be due to the widespread and increasing chloroquine resistance in Uganda, however the issue of chloroquine resistance was not investigated in the current study.

The prevalence of severe malaria anaemia in the study is lower than in Cameroon where it was 65% in children less than five years. The small sample size used in that study (20 children) could explain the higher value obtained.

5.2.2 Sickle Cell Anaemia

Sickle cell anemia was found amongst twelve children (13%) with severe anaemia and six children (6.5%) with non-severe anaemia. However the difference between the two groups was not statistically significant, (OR 2.15 CI 0.71 – 6.79).

One sickler had iron deficiency amongst the cases. Co-existence of severe iron deficiency in sickle cell patients has been reported in other studies.

This high prevalence of sickle cell anaemia is not surprising in a country where sickle cell carrier rate is 20%. Secondly the sickle cell clinic which has about 3000 patients is based in the same hospital, and sickle cell anaemia contributes to 14% of paediatric admissions. The prevalence in this study is similar to that in earlier studies in Mulago Hospital where sickle cell anaemia accounted for 14.5% of children admitted with severe anaemia. However, the prevalence in this study is lower than that in Ibadan, Nigeria where 17% of children in one hospital had severe anaemia and sickle anemia. This higher value could be because of the lower age group used (up to 2 years) as this is when anaemia is most common among sicklers from previous studies.
Secondly the standard of care of children with sickle cell anaemia improved with the establishment of the sickle cell clinic and day care centre for follow up where they are given antimalarial prophylaxis and folic acid as well as health education.

5.2.3 Iron deficiency anaemia

Overall, 19% of the 184 children had iron deficiency anaemia. Twelve children (13%) had iron deficiency anaemia amongst the group with severe anaemia. The iron status in these children was based on ferritin levels. Where there was inflammation, as indicated by C-reactive protein levels, higher cut-off points were used\textsuperscript{14}. Iron deficiency was more common among the controls than the cases, although the difference did not reach statistical significance (OR 0.45 CI 0.19 – 1.03; p-value = 0.060). A similar trend was noted using Coulter Counter values of mean cell hemoglobin concentration and mean cell volume. Iron deficiency was significantly more common among the controls than amongst the cases (OR 0.507 CI 0.273-0.941) The number of children on iron containing medication at the time of admission was 4 and 5 children among the cases and controls respectively. Therefore, this did not contribute to the higher number of children with iron deficiency among the controls. Other studies\textsuperscript{58, 13, 71}, however, have found much higher prevalence of iron deficiency amongst children in the same hospital with values ranging between 39.5% to 52%.

The lower prevalence in the current study could be because a large number of children (21%) had had previous blood transfusions and these children usually receive medication with iron and antihelminths as part of treatment on discharge (Appendix V). They are therefore less likely to have iron deficiency anaemia. The other explanation for the difference in values could be due to the superior method (ferritin levels) used to detect iron deficiency in the current study.

In the study done by Vanier,\textsuperscript{58} iron deficiency was based mainly on film reports which can be subjective and non-specific whereas in Wabwire’s study\textsuperscript{71} a higher cut off of subnormal serum ferritin levels (200 µg/l) was used, hence the higher values. Moreover,
Prevalence and Causes of severe anaemia in admitted children

hookworm infestation, previously an important cause of iron deficiency anaemia in some studies\(^8\) is no longer common in children under five years as evidenced by results of this study and other recent studies.\(^{13,71}\)

The prevalence of iron deficiency anaemia in this study is higher than that found in a community study in Kiyeyi, Uganda where iron deficiency anaemia was found in 18% of the children\(^{23}\). However the diagnosis of iron deficiency anaemia in that study was based on peripheral film reports and hemoglobin levels. Since these changes occur only in the late stages of iron deficiency, it is possible that the true prevalence of iron deficiency was under estimated.

5.2.4 Hookworm Anaemia

Hookworm ova were found in only one child (1.6%) amongst the cases and two children (2.2%) amongst the controls. All the hookworm infestations were light. It is known that the amount of blood loss in hookworm infestation is proportional to the number of adult worms, and the significance for hookworm infestation for anaemia is relevant at higher levels of infestation\(^63\). Thus hookworm infestation is unlikely to have contributed significantly to the aetiology of anaemia in these children.

This prevalence of hookworm in the current study is lower than in an earlier study done in Mulago Hospital\(^71\) where the prevalence was 4.5%. This is could possibly be due to the fact that the age group in that study\(^71\) was wider including children above 5 years and this is the group more affected by hookworm infestation\(^49\).

Similarly the prevalence in the current study is lower than that of rural community studies in Uganda of 32% and 45% in Kiyeyi Target area\(^23,74\). The age groups here involved children more than 5 years and this was a rural setting. Regular de-worming of children in urban areas by parents and medical staff could also have contributed to the low prevalence of hookworm, although no information was collected on this issue.
5.2.5 Other causes of severe anaemia

There were 22 children (23.9%) with severe anaemia and 25 children (27.2%) with non-severe anaemia whose aetiology of anaemia could not be established. Their clinical diagnoses included dysentery, suspected glucose 6 phosphate dehydrogenase enzyme deficiency and hypersplenism. However, one such child, (36 months old) presented with a one months history of anorexia and fever and was found to have pancytopenia, macrocytosis and hypoproteinemia. Bone marrow examination revealed megaloblastic erythropoiesis and no leukemic infiltrations. Megaloblastic anaemia was suspected but, unfortunately, tests for folate and Vitamin B\textsubscript{12} levels were not done as there are no facilities for their determination in Mulago Hospital. Another 24 months’ old child had marked hypochromia, microcytosis by film report and Coulter Counter and normal ferritin levels of 30 micrograms per litre. No further tests were done.

The former case brings in the role of megaloblastic anaemia in the causation of anaemia in children as reported by some authors\textsuperscript{47} while the latter case brings in other causes of microcytosis and hypochromia in absence of iron deficiency such as thalassaemia as indicated by some studies.\textsuperscript{76} It is possible that this child could have had thalassemia since the thalassemia gene has been documented among Ugandan children.\textsuperscript{77} Unfortunately confirmatory tests for thalassaemia and other causes of hypochromic microcytic anaemia such as lead toxicity could not be done in this study because of the high costs involved.
5.3 Clinical features amongst children admitted with severe anaemia.

The most frequent findings in the history and examination of the severely anaemic group of children were fever, difficulty in breathing, convulsions, a history of previous blood transfusions, hepatosplenomegaly, stunting, koilonychia and a gallop rhythm. On the other hand, the group with non severe anaemia frequently presented with fever, difficulty in breathing and convulsions. Only 7 (7.9%) had been transfused before. The frequent signs were hepatosplenomegaly and stunting.

There was a statistically significant higher number of children among the controls with a history of difficulty in breathing than among the cases. This can be explained by the fact that the study was carried out during the rainy season and therefore many children presented with respiratory tract infections. The finding of a statistically significant difference between the cases and controls in hepatomegaly and gallop rhythm as well as tender liver could be attributed to heart failure, in the severely anaemic group.

The finding of koilonychia or brittle nails having a statistically significant difference between the cases and controls even on logistic regression cannot be easily explained. However, one possibility could be that the nail changes in the presence of hypochromic anaemia are a late sign and occur in severe cases of anaemia.

Clinical findings in this study are similar to findings in other studies in Ibadan, Nigeria and Northern Ghana where fever and hepatosplenomegaly were still the major presenting complaints. This is not surprising given the fact that these are areas where malaria is endemic, and it is also the leading cause of severe anaemia and the above complaint are also common findings in malaria illnesses. Low birth weight, although implicated as an important finding amongst children with severe anaemia was not significant in this study where only 5 children had had low birth weight.
5.4 Type of anaemia

The majority of children presented with a hypochromic microcytic picture. There were 25 (27.2%) children in the severe anaemia group and 39 (42.4%) children in the group with non-severe anaemia. The difference between the two groups was statistically significant. There were 17 (18.5%) and 3 (3.3%) children with a macrocytic picture in the groups with severe and non-severe anaemia, respectively. A normocytic, normochromic picture was seen almost equally in both groups. A dimorphic picture 52 (56.5%) was seen more in the group with severe anaemia than in the group without severe anaemia.

Typing anaemia using the peripheral film was not used in this study apart from the result of the dimorphic picture because there was a lot of inter-observer variation. For instance, in regard to the hypochromic, microcytic picture, the result given was ranging from 67% to 98% in the group with severe anaemia, thus making analysis difficult.

Using the Coulter Counter, a hypochromic microcytic picture was shown to be more common in the non-severe anaemia group than the controls. This agrees with the finding of iron deficiency anaemia more common in the control group than in the cases. Further still there is a lot of hypochromic, microcytic anaemia not due to iron deficiency anaemia which could be caused by other diseases such as thalassemia and chronic illnesses. Clearly, there will be need to explore these issues in another study.

A dimorphic picture was seen in a 56.5% of children with severe anaemia in the present study which may indicate multiple aetiology as found by some authors. 22
5.5 Clinical causes of mortality in children with severe anaemia

The case fatality rate was 7.6% among the cases and 5.4% among the controls. The clinical cause of mortality in the severely anaemic group of children were reported as: pneumonia (5), cerebral malaria (1) and meningitis (1). Two children were reported to have died of cerebral malaria despite a negative blood slide for malaria. None of the children in the severely anaemic group had an autopsy. All children apart from one died within 48 hours of admission and they were all less than 2 years. Five of them had received blood transfusion, and four of the children were in congestive heart failure. Three children had kwashiorkor, and 4 children had P.falciparum parasitaemia.

In the group of children with non-severe anaemia, the causes of death were: pneumonia (1) cerebral malaria (1) and meningitis (1). The cause of death was not established in two children.

The case fatality rate and the clinical cause of death in this small series is higher than the 6.1% rate in an earlier study done at the same hospital. The cause of mortality is also different in that in the previous study, hookworm was reported to be the major cause followed by sickle cell anaemia. However, hookworm is no longer an important cause of anaemia in children less than 5 years. 

The case fatality rate in the present study is lower than the 29.3% found in a study in Kenya. The leading causes of death were reported as malaria (12.2%), followed by bacteremia (8.7%), malnutrition (0.8%) and pneumonia (2.4%).

The difference in the case fatality rate could be explained by the fact that children were followed up even after discharge in the Kenyan study hence the higher values. The clinical causes of mortality however are similar to those in the present study. It is difficult to confirm the cause of deaths since autopsy was not done in all children. Similarly, the presence of pneumonia in severely anaemia children is difficult to confirm since no radiological diagnosis was done.

However, respiratory distress is a major risk factor for death in children with malaria. It is also known from previous studies that respiratory distress in a severely anaemic child is commonly due to acidosis resulting from inadequate oxygen delivery to poorly perfused tissues and not necessarily due to heart failure or pneumonia.
5.6 LIMITATIONS

1. Serum ferritin concentrations are elevated in malaria and inflammatory conditions\(^\text{18}\). This could have caused an underestimation of the prevalence of iron deficiency in these patients. To reduce this limitation, serum ferritin levels were adjusted for inflammation.

2. Results of this study may not be generalisable to the Ugandan population because it is a hospital-based study.

3. Some children with severe anaemia came late in the night and were missed because the laboratory facilities were not available at that time.

4. Other contributing factors to severe anaemia such as HIV\(^\text{23,24}\), enzyme deficiencies, autoimmune anaemia and folate levels were not investigated in this study because of financial constraints.

5. Differentiation of iron deficiency from thalassaemia could not be done using red cell distribution width because the hospital Coulter Counter machine was not operational at the time. Bone marrow staining for iron was not done. However, some studies have shown that absence of stainable iron in the bone marrow is not diagnostic of iron deficiency\(^\text{20}\). It is also an invasive procedure highly subjective and difficult to quantify.
6.1 CONCLUSIONS

1. The prevalence of severe anaemia (21.4%) amongst children admitted to Mulago Hospital is unacceptably high.

2. Malaria is the major cause of severe anaemia (58.7%) followed by sickle cell anaemia (13%) and iron deficiency (13%)

3. One in five children (20.7%) with severe anaemia had a history of previous blood transfusions.

6.2 RECOMMENDATIONS

1. Given the high prevalence of severe anaemia necessitating blood transfusions, there is need to reinforce measures for preventing malaria so as to reduce the frequency of severe anaemia in children.

2. There is need for a detailed prospective clinical audit of children admitted with severe anaemia in Mulago Hospital involving a higher number of children.

3. There is need for a more detailed study to identify other causal factors in children with severe anaemia such as folate deficiency, G6PD deficiency, HIV, thalassaemia, and lead.
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57. Lozoff B, Jimerez E, Mollen J et al. Poorer behavioral and developmental outcome more than ten years after treatment for iron deficiency in infancy. *Paediatrics* 105:E51


63. WHO Bench and for diagnosis of intestinal parasites; 1994:13


CONSENT FORM

SEVERE ANAEMIA STUDY

MAKAREERE UNIVERSITY DEPARTMENT OF PAEDIATRICS AND CHILD HEALTH – MULAGO.

Title: Severe anaemia among children presenting to ACU.

Principal Investigator
Dr. Nakiboneka Deborah
Makerere University
Telephone: 077 467397

Purpose
You are being asked to have your child participate in a research study that aims at finding out the prevalence, and some common causes of severe anaemia in children. Anaemia is not having enough blood in the body. In Uganda anaemia, is a major health problem. It can be caused by diseases such as malaria, sickle cell, worm infestations and lack of certain nutrients. This research is being carried out to improve its management. About 1400 children will participate in the study.

Study procedure:
As part of this research, you will be asked questions about your child’s health, and he/she will be examined for anaemia.

During the study, doctors or their staff will ask you:
1. to answer questions about your child’s health
2. to have your child examined for signs of severe anaemia
3. to have your child’s samples of blood and stool taken for examination in the laboratory to look for the possible cause of severe anaemia in him or her.

About 2 teaspoonfuls of blood will be removed from your child’s vein.

Your child will receive all the usual care and treatment for severe anaemia and any concurrent infection.
**Prevalence and Causes of severe anaemia in admitted children**

**Benefits**
If you agree to take part in this research study you will be able to know more about your child’s health such as presence or absence of sickle cell disease. All the tests will be done free of charge.

**Risks**
Having blood drawn may cause some pain, bleeding or bruising where the needle enters the body and rarely may cause infection. Treatment for this is available.

**Confidentiality**
Your child’s research records will be kept confidential to the extent allowed by law. Only the people working on the study will see it. A study number which will only be known to you and the study personnel will be used instead of your child’s name during analysis. This number will be shared only with those individuals who need to know because they are working on this study. The code numbers will be kept in a safe place. Only the study personnel will have access to your child’s medical records and personal identifiers. Personal identifiers will not be included in the analysis.

**Voluntary Statement**
Accepting your child to participate in this study is completely voluntary, and that you may stop him/her taking part in the study at any time. It is entirely up to you whether or not to have your child participate in this study. Withdrawing the child from the study will not stop the child from getting standard care.

**Consent**
The purpose, risks and benefits of this study have been explained to me. I have read this form or had it read to me in my language and feel that I had enough time to consider my decision to join the study.

**Description of studies**
I understand that if I have any questions, I may ask them now or at any time during the study. I may ask to speak with Dr. Nakiboneka (Tel: 077 467397) or her colleagues at Mulago hospital. I understand that a copy of this form will be kept in my child’s study file.

I understand that by signing below or making a thumb print, I have understood the purpose, procedure, benefits and risks of the study. I agree to join the study and follow the study procedures to the best of my ability. I freely agree to join the study.

Name of child

Name of parent / guardian ________________________ Signature ________________________

Date ______/_____/____

Study ID [_______] [_______] [_______]

IP No. ________________________
FORM B
SEVERE ANAEMIA STUDY
QUESTIONNAIRE
CLINICAL EXAMINATION SHEET

Date: .............................................................

Child’s particulars
Serial No......................................................... IP No. ......................
Name: ........................................................................

1. Age (months) ......................................................
2. Sex: Male / Female
3. Tribe: .....................................................................
4. Village: .................................................................
5. Sub-county: ..........................................................
6. County: ..................................................................
7. District: ..................................................................
8. Birth weight: ..................................................... Term/Premature

Present Complaint:                                Duration (days)
1. Fever [ ] .........................................................
2. Fast or difficult breathing [ ] ..........................
3. Loss of appetite [ ] ..............................................
4. Irritability [ ] ....................................................
5. Vomiting [ ] ......................................................
6. Convulsions [ ] ...................................................
7. Bloody Diarrhea [ ] ............................................
8. Loss of consciousness [ ] .................................
9. Easy fatiguability [ ] ..........................................
10. Sore mouth [ ] ..................................................

Coding
1 = Yes
2 = No
3 = Do not know
Prevalence and Causes of severe anaemia in admitted children

<table>
<thead>
<tr>
<th>No.</th>
<th>Symptom</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Yellow eyes</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Passing Red/tea colour urine,</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Joint swelling</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Easy bruisibility</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Black stool / Bloody stool</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Pica</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Others (Specify)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Vaccination (upToDate)</td>
<td></td>
</tr>
</tbody>
</table>

**Past history**

1. Drug / Herb ingestion / Toxin exposure [ ]
   Specify                        

2. Passing worms                  

3. Previous blood transfusion [ ]
   Specify number and date

4. Previous admission [ ]
   Specify number and date

5. Neonatal jaundice [ ]

6. Neonatal bleeding [ ]

**Nutritional Study**

1. Is / was child breast fed? [ ]

2. Age of weaning ................ months

Current diet

1. Solid food Specify

2. Sauce Specify

3. Greens Specify

4. Liquid feeds / Gruel. Specify

5. Fruits Specify
Family history
1. Number of children
   a.) alive
   b.) dead

2. Anaemia
   [  ]
3. Sickle cell anaemia
   [  ]

Social history
1. Mother’s occupation Specify
2. Father’s occupation Specify
3. Mother’s level of education
   a) No formal education [  ]
   b) primary level [  ]
   c) ‘O’ level [  ]
   d) ‘A’ level [  ]
   e) Tertiary [  ]
3. Father’s level of education
   a) No formal education [  ]
   b) primary level [  ]
   c) ‘O’ level [  ]
   d) ‘A’ level [  ]
   e) Tertiary [  ]

Physical Examination
1. Weight ......................... (kg)
2. Height/Length ......................... (cm)
3. Temperature ......................... (°C)
4. General Condition
   a.) Well [  ]
   b.) ill [  ]
   c.) Very ill [  ]
5. Visible wasting
   a.) None [  ]
   b.) Mild [  ]
   c.) Moderate [  ]
   d.) Severe [  ]
6. Pallor
   a.) Nil [  ]
   b.) Mild [  ]
Prevalence and Causes of severe anaemia in admitted children

c.) Moderate [ ]
d.) Severe [ ]

7. Jaundice
e.) Nil [ ]
f.) Mild [ ]
g.) Moderate [ ]
h.) Deep [ ]

8. Skin and nails
a.) Petechiae [ ]
b.) Bruises [ ]
c.) Echymoses [ ]
d.) Koilonychia/Brittle nails [ ]

9. Lymphadenopathy [ ]
Specify size ......................
Site ......................

10. Bone tenderness [ ]
11. Pedal Oedema [ ]

Respiratory System
Respiratory rate .................... (b/min.)
Chest indrawing [ ]
Nasal flaring [ ]
Breath sounds
a.) Normal [ ]
b.) Vesicular [ ]
c.) Bronchial breathing [ ]

Added sounds
a.) Rhonchi [ ]
b.) Crepitations [ ]
c.) Pleural rub [ ]
Prevalence and Causes of severe anaemia in admitted children

Cardiovascular System
Blood pressure .................. mmHg
Heart rate .................. (beats/min)
JVP raised [ ]
Heart sound
a.) Normal [ ]
b.) Gallop [ ]
Abdomen
Liver
a.) Tender [ ]
b.) Size ................. cm
Spleen
a.) Tender [ ]
b.) Size ................. cm
Central Nervous System
State of consciousness
Modified Glasgow Coma Scale
a.) 3 [ ]
b.) 4 [ ]
c.) 5 [ ]
d.) 6 [ ]
e.) 7 [ ]
f.) 8 [ ]
m.) 15 [ ]
j.) 9 [ ]
h.) 10 [ ]
i.) 11 [ ]
j.) 12 [ ]
k.) 13 [ ]
l.) 14 [ ]

Treatment on admission
Blood transfusion [ ]
Antimalarial [ ]
Specify .........................
Antihelminthic [ ]
Specify .........................
Haematinics [ ]
Specify ......................... Diagnosis on admission .........................
Final diagnosis .........................

Outcome
Death [ ]
Clinical cause of mortality (specify) ........................................
Date of discharge / death ..........................
FORM C
SEVERE ANAEMIA STUDY

Serial No. ......................  IP No. .................
Name: ............................ Age ......................

LABORATORY INVESTIGATIONS

Blood
1. Hb ........................... (g/dl)
2. RBC (total) .................... x 10^6/ul
3. WBC (total) .................... x 10^3/ul
4. PCV ........................... (%)
5. MCV ........................... (fl)
6. MCHC ........................... (g/dl)
7. MCH ........................... (pg)
8. Reticulocyte count ............... (%)
9. Reticulocyte Index ..............

Blood Film report

a) Erythrocyte hemoglobinisation
1. Hypochromia   [  ]
2. Normochromia  [  ]
3. Polychromasia  [  ]

b) Erythrocyte size
1. Microcytosis   [  ]
2. Normocytosis   [  ]
3. Macrocytic     [  ]
4. Anisocytosis   [  ]

c) Red blood cell shape (Significant number)
1. Normal        [  ]
2. Sickle cell    [  ]
3. Target cells [ ]
4. Acanthocytes [ ]
5. Poikilocytes [ ]
6. Schistocytes [ ]
7. Elliptocytes [ ]
8. Teardrop cells [ ]
9. Helmet cells [ ]
10. Other (specify) .....................

d) Malaria parasites
   Species Specify .....................
   Parasite density ....................
   Any other comment ..................

Hb electrophoresis
   a.) Hb AA [ ]
   b.) Hb AS [ ]
   c.) Hb SS [ ]
   d.) Other Specify ....................

Biochemistry
1. Serum ferritin ....................... μ/l
2. C – Reactive Protein ............... mg/dl

Stool Analysis
a. Macroscopy
   1. Bloody [ ]
   2. Consistency ......................

b. Microscopy
   1. Red blood cells [ ]
   2. Ova/cysts [ ]
      If yes, specify ..................

c. Occult blood (guaic test)
   1. Positive [ ]
   2. Negative [ ]
Appendix iv

**Blood Indices** \(^{14}\) [Normal ranges (N)]

These were done using a Coulter Counter.

If less than 5gd/l it was regarded as severe anaemia.

MCV \(N = 80-95\) fl.

MCHC \(N = 30-35\) g/dl

MCH \(N = 27-34\) pg

PCV \(N = 40-52\)

Platelet Count \(N = 150-400 (10^9/l)\)

WBC \(N = 6-18 (10^9/l)\)

RBC \(N = 4.5-6.5 (10^{12}/l)\)

Reticulocyte Index \(N = 1.5\)

Reticulocytes \(N = 0.5-2.0\%\)

Absolute count \(25-75 \times 10^9/l\)
Appendix v

PAEDIATRIC GUIDELINES TO MANAGEMENT OF SEVERE ANAEMIA IN ACU

INVESTIGATION
The tests in bold print should always be done before a transfusion!
- **Haemoglobin concentration** (Cyanmethaemoglobin method)
- **Blood film** Malaria parasites
  - RBC: hypochromia, microcytosis, anisocytosis (Iron deficiency, thalassaemia)
  - WBC: hypersegmented neutrophils (Folate, Vit B12 deficiency)
  - RBC: sickle cells
  - RBC: target cells (Thalassaemia, iron deficiency)
- **Mean Corpuscular Volume** (MCV) and reticulocyte count as the two principal criteria for the initial classification of anaemia
- Haemoglobin electrophoresis: Sickle cell, Thalassaemia
- Red cell volume distribution (RDW) index is a useful criterion of classification alongside MCV. This can be measured with automated red cell analysers (Coulter counter) in Mulago. RDW index reflects the heterogeneity of the red blood cell size and thus provides a quantitative measure of anisocytosis.
- Stool test, Parasitic ova, blood
- Haematocrit or PCV (microcentrifuge)

MANAGEMENT
a) Establish diagnosis and severity of anaemia
b) Treat malaria (oral route)
   1\(^{st}\) line: Chloroquine 10 mg/kg day 1 & 2, then 5 mg/kg day 3 (total dose 25 mg/kg)
   2\(^{nd}\) line: Fansidar (contraindicated in G6PD deficiency)
      One tablet contains sulfadoxine 500 mg and Pyrimethamine 25 mg
      \[
      \begin{array}{ll}
      \text{AGE or WEIGHT} & \text{TABLET} \\
      \text{2-12 Months (4-10 kg)} & \frac{1}{2} \text{tablet} \\
      \text{1-5 years (10-19 kg)} & 1 \text{tablet} \\
      \text{5-9 years (19-26 kg)} & \frac{1}{2} \text{tablets} \\
      \text{9-14 years (26-36 kg)} & 2 \text{tablets} \\
      \text{> 14 years} & 3 \text{tablets stat dose} \\
      \end{array}
      \]
   3\(^{rd}\) line: Quinine, for severe malaria or no response (see cerebral malaria guidelines for iv preparation): oral 10 mg/kg 8 hourly for 7 days.
c) Haematinics (oral route)
   - Folic acid
   - Up to 5 years 2.5 mg once daily
   - > 5 years 5 mg once daily

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Prevalence and Causes of severe anaemia in admitted children

Iron

<table>
<thead>
<tr>
<th>Age or weight</th>
<th>Ferrous sulphate 200 mg (60 mg elemental iron)</th>
<th>Ferrous fumarate 60 mg per 5 ml (12 mg elemental iron/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 months (4-6 kg)</td>
<td>-</td>
<td>2 ml</td>
</tr>
<tr>
<td>4-12 months (6-10 kg)</td>
<td>-</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>1-3 years (10-14 kg)</td>
<td>½ tablet</td>
<td>4 ml</td>
</tr>
<tr>
<td>3-5 years (14-19 kg)</td>
<td>½ tablet</td>
<td>5.5 ml</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>1 tablet</td>
<td></td>
</tr>
</tbody>
</table>

Iron or folic acid should be given once daily for two months.

d) Antihelminthics

Albendazole - drug of choice if available
- 400 mg as a single dose (200 mg if child < 2 years)
Mebendazole - effective against hookworm and trichuris trichuria (whipworm)
- for children over 1 year
- 250 mg as single dose (or 500 mg when the child is above 2 years)
- may be repeated after 2 or 3 months

Pyrantel - effective against hookworm
- 10 mg/kg (max 1 g) as a single dose

e) Blood transfusion.

Indications:  
1. Severe anaemia (Hb < 5 g/dl) with impending or overt cardiac failure e.g. due to malaria.
2. Hyperparasitaemia in malaria if Hb < 6 g/dl
3. In sickle cell disease
   a) if Hb < 5 g/dl or severe infection present
   b) CVA (regardless of Hb)
   c) Priapism (regardless of Hb)
4. Children in congestive cardiac failure due to severe anaemia
5. Severe chronic haemolytic anaemia such as Thalassaemia major
6. Following acute severe blood loss – remember that the Hb can initially be normal!

VOLUME OF TRANSFUSION
GIVE WHOLE BLOOD

20 ml/kg

or

Required volume (ml) = weight (kg) x 3 x desired rise in Hb (g/dl)

In both cases, rate = 3 ml/kg/hour

Add frusemide 1 mg/kg iv immediately in advance of transfusion to avoid precipitating cardiac failure.