BACTERIAL INFECTIONS IN CHILDREN IN SICKLE CELL CRISIS

AT

THE KENYATTA NATIONAL HOSPITAL

A dissertation submitted in part-fulfilment for the degree of

MASTER OF MEDICINE (PAEDIATRICS AND CHILD HEALTH)

of the

UNIVERSITY OF NAIROBI, KENYA

by

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DECLARATION

This dissertation is my original work and has not been presented for a degree in any other University.

signed ................................
(DR. F. ESAMAI)

This dissertation has been submitted for examination with my approval as University Supervisor.

signed ................................
(DR. J. S. MEME)
<table>
<thead>
<tr>
<th>CONTENTS</th>
<th>PAGE NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMARY</td>
<td>A1</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>MATERIALS &amp; METHODS</td>
<td>3</td>
</tr>
<tr>
<td>RESULTS</td>
<td>7</td>
</tr>
<tr>
<td>DISCUSSION AND REVIEW OF THE LITERATURE</td>
<td>15</td>
</tr>
<tr>
<td>CONCLUSION</td>
<td>24</td>
</tr>
<tr>
<td>RECOMMENDATIONS</td>
<td>25</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>26</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>27</td>
</tr>
<tr>
<td>Table I - Age distribution of the 40 patients</td>
<td>.......... 8</td>
</tr>
<tr>
<td>Table II - Distribution of the 40 patients according to Clinical diagnosis and of the various organisms isolated</td>
<td>.......... 9</td>
</tr>
<tr>
<td>Table III - Age distribution of the 18 bacteriologically positive cases</td>
<td>.......... 10</td>
</tr>
<tr>
<td>Table IV - Distribution of the bacteriological cultures according to site of isolation</td>
<td>.......... 10</td>
</tr>
<tr>
<td>Table V - Age distribution of the 40 patients according to crisis</td>
<td>.......... 11</td>
</tr>
<tr>
<td>Table VI - Haematological parameters of the 40 patients according to crisis (means and standard deviations)</td>
<td>.......... 13</td>
</tr>
</tbody>
</table>
SUMMARY.

This is a prospective study of forty children in sickle cell crisis with suspected bacterial infections seen at the Kenyatta National Hospital, Nairobi.

Eighteen of these children were found bacteriologically positive on various cultures of blood, urine, stool and throat swabs.

The bacteriological data, age distribution and haematological data are presented and discussed.

From this study its apparent that bacterial infections are a common cause of hospitalisation of children with sickle cell disease especially in those under six (6) years of age and that respiratory tract infections is the commonest reason for hospitalisation of these children.
INTRODUCTION.

Patients with sickle cell disease (Hbss) commonly suffer from painful crises and haematological crisis. Painful crisis is characterised by musculoskeletal or abdominal pain attributed to the long jam sickled erythrocytes in small blood vessels. Bone and pulmonary infarction, renal disfunction, priapism, leg ulcers and a variety of neurological sequelae are well known complications of associated tissue anoxia, thrombosis and necrosis.

Accelerated anaemia due to Red Blood Cell Sequestration or hyperhaemolysis may complicate painful crisis but haematological crisis typically appear separately and are due to transient depression of bone marrow (1, 2, 3, 4).

Infection and not crisis is the most common cause of death particularly in children (5, 6, 7, 8, 9). The frequency of infection in hospitalised patients with sickle cell disease has led to the dual hypothesis that these patients are unduly susceptible to infections and that infection commonly precipitates crisis (10, 11, 12, 13, 14). While no infection is found with
majority (1, 15), subclinical infection has been postulated on the basis of infection in other members of the family at the time of crisis in siblings or simultaneous crisis in affected members of a family (16, 17, 18). Support for fever induced crisis is provided by the frequency of crisis following febrile transfusion reactions (13), and by increased sickling associated with pyrexia of typhoid immunisations in patients with sickle cell trait (12).

Also prevention of febrile disease by regular doses of long acting penicillins and chloroquine reduced clinical crisis and improved haematological picture in African children (20).

There are however very few convincing reports of crisis associated with proven bacterial infection especially in developing countries. However documented infection does not always induce crisis (1, 15), thus the actual risk or relative importance of bacterial infection in the causation of frequent crisis or early death is unknown (22).

It is with these facts in mind that the author undertook to carry out this study with the following aims and objectives.

AIMS AND OBJECTIVES.

To establish the types of bacterial infections in children in sickle cell crisis and the distribution of these infections.

To establish the age distribution of patients in sickle cell crisis.
MATERIALS AND METHODS:

The study was carried out at the Kenyatta National Hospital in-patients services which comprises the paediatric observation ward, wards 7 to 10 and the Block III of the Infectious Disease Hospital. The study was done over a nine month period July, 1982 to March, 1983.

The criteria for selection of patients into the study were:

1. All patients proven by citrated Acetate Paper Electrophoresis to be homozygous for sickle cell disease presenting in clinical crisis. The haemoglobin electrophoresis was either done in a previous admission or in the haematology clinic of the hospital, but this was however repeated in all the patients on admission.

2. All children in sickle cell crisis who present with a probable bacterial infection aged 12 years and below. The age was ascertained from the parent or guardian on interview or on production of a birth certificate whenever this was possible.

3. Patients were admitted into the study on Mondays, Wednesdays and Fridays of every week during the study period. Every child seen for each particular day was included.

4. Patients who had not been previously diagnosed to be suffering from sickle cell disease and gave a history of blood transfusion within the last three months were excluded from the study.
5. All patients proven to have malaria infection on admission and during the study were excluded from the study.

6. All patients who had received antibiotic therapy from a peripheral hospital before admission to the hospital were excluded from the study.

The author then interviewed all the parents or guardians of the children and carried out a systematic physical examination on all the children. An informed consent was obtained from all the parents or guardians accompanying the patient for the child to be included in this study. A written consent was obtained from the Ethical Committee of the Hospital.

The following investigations were performed on all the children:

I. A venepuncture was performed to obtain a total of 12 ml of venous blood. The skin at the site of venepuncture was cleaned with sterile swabs soaked in 70% alcohol. Dry disposable 20 cc syringes and 23 gauge syringes were used for this procedure. The needles were changed between venepuncture and inoculation of blood into the culture transport media bottles. 5 ml of blood was inoculated into each of the bottles; one for aerobic cultures containing Thiol Dextrose Phosphate broth and one for anaerobic cultures containing sodium Thioglycollate. These were then sent immediately to the Microbiology Laboratory of the Hospital.
Standard Methods were used for bacteriological cultures and sensitivity testing, by a microbiologist (41, 42). Three sets of blood cultures were obtained within the first 24 hours of admission.

II. The remaining 2 ml of blood was sent to the Haematology Laboratory in a sequestrated bottle. A haemogram using a coulter counter machine was performed; a haematologist did a peripheral blood film for white blood cell differential count; reticulocyte count; erythrocyte sedimentation rate, haemoglobin electrophoresis and malaria parasites using standard haematological methods (43, 44).

III. A clean catch urine specimen was obtained in all children on admission. The vulva or glans penis were cleaned with sterile swabs soaked in normal saline. For females the vulva was cleaned twice in the antero-posterior direction and finally wiped with dry sterile swabs. Paediatric adhesive urine collectors were then taped onto the external genitalia. In older children the above procedure was demonstrated to the parent and the patient and were then asked to provide the urine specimen thereafter. The urine was sent in a sterile bottle to the Microbiology Laboratory within 30 minutes of collection. The urine was analysed for protein, sugar, red blood cells, pus cell: and a culture and sensitivity testing was performed for all urine specimens. Standard methods were used (41, 42).
The following investigations were done on patients in whom the clinical presentation necessitated these to be done.

I. Throat swabs using sterile fresh wet serum swabs. These were taken in all those children who were found to have purulent pharyngitis and/or tonsillitis on examination of the throat. The tongue of the child was depressed with a wooden tongue depressor and without touching the buccal mucosa or tongue the serum swab was rotated deeply around the pharynx and tonsils. These were immediately sent to the Microbiology Laboratory for bacteriological cultures using Standard Methods (41, 42).

II. A stool specimen was collected in those children who presented with diarrhoea as the main and only presenting complaint. This was sent in a sterile plastic bottle for bacteriological cultures.

III. A lumbar puncture was done in those children who presented with features of meningitis on clinical examination. The cerebrospinal fluid was sent to the Microbiology Laboratory in a sterile cerebrospinal fluid bottle for culture and sensitivity using standard methods. Another sample was sent to the Chemical pathology laboratory in a fluoride bottle for sugar and protein estimation. (41, 42).
IV. Chest radiographs were done in all cases of pneumonia and specific bone radiographs were done in cases of suspected osteomyelitis. A radiologist interpretation was sought in all these cases.

The author then categorised these patients into the various types of clinical crises according to the classification of Rolant Scott (34).

RESULTS

There were a total of 40 patients in this study. There were 28 males and 12 females. 31 (77.5%) of the patients were of the Luo Ethnic group; 6 (15%) were Lukhya while the Girama, Kamba, and Kisii accounted for 1 case each (2.5%).

AGE DISTRIBUTION.

The majority of the patients were in the age group 4 - 6 years in which there were 17 patients (42.5%) (Table I).
TABLE I. AGE DISTRIBUTION OF THE 40 PATIENTS

<table>
<thead>
<tr>
<th>AGE (YEARS)</th>
<th>NO. OF PATIENTS</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>10</td>
<td>25.0</td>
</tr>
<tr>
<td>4-6</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td>7-9</td>
<td>10</td>
<td>25.0</td>
</tr>
<tr>
<td>10-12</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>TOTAL</td>
<td>40</td>
<td>100.0</td>
</tr>
</tbody>
</table>

CLINICAL DIAGNOSIS AND BACTERIOLOGICAL DATA.

The commonest reason for hospitalisation was respiratory tract infections accounting for 20 of the 40 patients (50%). Pharyngotonsillitis accounting for 10 and pneumonia for the other 10 (Table II).

There were a total of 18 bacteriologically positive cases. There were 9 positive cases from the 10 cases of pneumonia while 3 positive cases of the 10 patients with pharyngotonsillitis (Table II).

The three cases of meningitis also had pneumonia and the same organisms were isolated from blood and cerebrospinal fluid in each of the patients. The distribution of the Clinical diagnosis and bacterial organisms is shown in Table II.
<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>No. of Patients</th>
<th>%</th>
<th>Organisms Isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngotonsillitis</td>
<td>10</td>
<td>25.0</td>
<td>2 Staph. Aureus 1 Strep. Pyogenes</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10</td>
<td>25.0</td>
<td>3 Strep. Pneumonia 2 Staph. Aureus 2 Salm. Typhimurium 1 Strep. Pyogenes 1 Klebsiella</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>8</td>
<td>20.0</td>
<td>1 Salm. Typhimurium</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>4</td>
<td>10.0</td>
<td>2 Staph. Aureus 1 Strep. Pneumonia</td>
</tr>
<tr>
<td>*Meningitis</td>
<td>3</td>
<td>7.5</td>
<td>*2 Strep. Pneumonia *1 Klebsiella</td>
</tr>
<tr>
<td>Bacillary Dysentery</td>
<td>1</td>
<td>2.5</td>
<td>1 Shigella Sonnei</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>1</td>
<td>2.5</td>
<td>1 E. Coli</td>
</tr>
<tr>
<td>Pyogenic Axthritis</td>
<td>1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Impetigo</td>
<td>1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>40</td>
<td><strong>100.0</strong></td>
<td>21</td>
</tr>
</tbody>
</table>

* The 3 cases of Meningitis also have positive blood cultures
There were 10 positive cases in the age group 4-6 years and 4 in the age group 0-3 years (Table III).

**TABLE III AGE DISTRIBUTION OF THE 18 POSITIVE CASES.**

<table>
<thead>
<tr>
<th>AGE (YRS)</th>
<th>NO. OF +VE CASES</th>
<th>NO. OF -VE CASES</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>4-6</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Over 7 yrs.</td>
<td>4</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>18</strong></td>
<td><strong>22</strong></td>
<td><strong>40</strong></td>
</tr>
</tbody>
</table>

From this table there is no statistical significance in the distribution of the organism for the three age groups, (P > 0.05).

Of the 18 positive cultures 12 of these (66.7%) were from blood and the remaining were either from throat swabs, stool or urine (Table IV).

**TABLE IV. DISTRIBUTION OF THE SPECIMENS AND ISOLATED ORGANISMS.**

<table>
<thead>
<tr>
<th>SPECIMEN</th>
<th>NO. OF PATIENTS</th>
<th>%</th>
<th>ORGANISMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOOD</td>
<td>12</td>
<td>66.7</td>
<td>5 STREP. PNEUMO 3 STAPH. AUREUS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 SALM. TYPHIMURIUM 1 STREP. PYOGENES 1 KLEBSIELLA</td>
</tr>
<tr>
<td>THROAT</td>
<td>3</td>
<td>16.7</td>
<td>2 STAPH. AUREUS 1 STREP. PYOGENES</td>
</tr>
<tr>
<td>STOOL</td>
<td>2</td>
<td>11.0</td>
<td>1 SALM. TYPHIMURIUM 1 SHIGELLA SONNEI</td>
</tr>
<tr>
<td>URINE</td>
<td>1</td>
<td>5.6</td>
<td>1 E. COLI</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18</td>
<td>100.0</td>
<td>18</td>
</tr>
</tbody>
</table>
The gram positive organisms accounted for 12 (66.6%) of the cases while the gram negative organisms accounted for the rest (33.4%). The streptococcus pneumonia and staphylococcus aureus accounted for 27.8% each; followed by salmonella typhimurium 16.65%; streptococcus pyogenes 11% while klebsiella, E.Coli and Shigella accounted for 5.55% each.

CRISIS DISTRIBUTION:

Thrombotic crisis accounted for 24 of the 40 patients (60%). The distribution according to crisis and age is shown in Table V.

<table>
<thead>
<tr>
<th>AGE YRS</th>
<th>THROMBOTIC</th>
<th>MIXED</th>
<th>HAEMOLYTIC</th>
<th>APLASTIC</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>4-6</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>7-9</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>10-12</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>24</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>40</td>
</tr>
</tbody>
</table>

HAEMATOLOGICAL PARAMETERS

The haematological parameters of all the 40 patients have been divided according to crisis (Table VI).

(a) Haemoglobin

The mean haemoglobin level was 7.41 g/dl for thrombotic crisis patients; 5.49 g/dl for mixed crisis, 5.62 g/dl and 5.86 g/dl for haemolytic and aplastic crises respectively.
The means and standard deviations are shown in Table VI.

(b) **Total white cell count:**

The overall mean white cell count was 17700 per cu mm.

The means and standard deviations for the various types of crisis are shown in Table VI.

(c) **Erythrocyte Sedimentation rate.**

This is elevated in all types of crisis but not higher than 10 mm/hr.

(d) **Reticulocyte Counts:**

There was reticulocytosis of between 7% and 10% in all types of crisis except for aplastic crisis where there is a reticulocytopenia.

(e) **Polymorphonuclear Leucocytes:**

In all the types of crisis there was a polymorphonuclear leucocytosis as shown in Table VI. The absolute counts are all greater than 10,000 per cu mm except for patients in aplastic crisis. The absolute mean average for the 40 patients was 11,310 per cu mm.
TABLE VI.

HAEMATOLOGICAL PARAMETERS OF THE 40 PATIENTS ACCORDING TO CRISIS (MEANS AND STANDARD DEVIATIONS).

<table>
<thead>
<tr>
<th>CRISIS</th>
<th>Mean Hb g/dl</th>
<th>Mean WBC x 10^3/cu mm</th>
<th>Mean ESR mm Hr.</th>
<th>Mean Retic %</th>
<th>Mean Polys %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hb</td>
<td>WBC</td>
<td>ESR</td>
<td>Retic</td>
<td>Polys</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>THROMBOTIC</td>
<td>7.41</td>
<td>20.20</td>
<td>28.9</td>
<td>6.58</td>
<td>66.7</td>
</tr>
<tr>
<td>n = 24</td>
<td>1.16</td>
<td>5.26</td>
<td>15</td>
<td>0.58</td>
<td>12.69</td>
</tr>
<tr>
<td>MIXED</td>
<td>5.49</td>
<td>15.58</td>
<td>19</td>
<td>8.56</td>
<td>67.25</td>
</tr>
<tr>
<td>n = 8</td>
<td>1.62</td>
<td>3.08</td>
<td>8.62</td>
<td>1.85</td>
<td>6.39</td>
</tr>
<tr>
<td>HAEMOLYTIC</td>
<td>5.62</td>
<td>16.86</td>
<td>16.2</td>
<td>9</td>
<td>58</td>
</tr>
<tr>
<td>n = 5</td>
<td>1.46</td>
<td>2.00</td>
<td>9.01</td>
<td>1</td>
<td>10.93</td>
</tr>
<tr>
<td>APLASTIC</td>
<td>3.86</td>
<td>10.06</td>
<td>15</td>
<td>0</td>
<td>48.67</td>
</tr>
<tr>
<td>n = 3</td>
<td>0.42</td>
<td>3.48</td>
<td>8.66</td>
<td>0</td>
<td>26.83</td>
</tr>
<tr>
<td>STATISTICAL</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.01</td>
<td>P &gt; 0.01</td>
<td>P &lt; 0.01</td>
<td>P &gt; 0.01</td>
</tr>
<tr>
<td>SIGNIFICANCE</td>
<td>EX^2 test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
From this table we see that there is significant statistical difference in all the types of crisis in the level of haemoglobin, white blood cell total counts and reticulocyte counts but no statistical significance in the erythrocyte sedimentation rates and polymorphonuclear leucocytes among the types of crisis.
Sickle cell disease is prevalent among the Negro population of the world. In Kenya it is found among the Luo and Luhyia ethnic groups living around Lake Victoria as evidenced by the tribal distribution shown in the results of this study. It's also found among the Arabic Kinsmen of the Coast viz the Girama. A few cases are found among the Kamba and Kisii tribesmen, but with the increasing intermarriage this is bound to spread to other tribes as generations pass by.

This study was carried out in Nairobi which comprises a mixed ethnic society and the findings may not portray the same picture that would be seen if this study were carried out in a rural setting in the Western Region of Kenya if given similar facilities. The findings of this study may also be modified by a better socio-economic status of the Nairobi Urban population that was selected with a better income and sanitary environment than the rural population that is found in the Western region of the country where majority of the children with sickle cell disease normally reside and thus prone to overwhelming and fatal infections. This is made even worse by the distant health institutions and lack of adequate facilities for diagnosis and drugs.

A controlled study could not be carried out for this study for various reasons. First, is the absence of an appropriate control in that stable state sickle cell patients would not be useful as no bacterial organisms would be obtained for comparisons and even the sickle cell disease. Children not in crisis with probable bacterial infection would not make an ideal control group because
crisis does not change the organisms in the environment and infection with differentiation between crisis and infection without crisis is so diffuse that it would practically be not possible to undertake without intermixing, although this would appear theoretically easy.

Secondly proof of bacterial infection as a precipitant of crisis has not been documented biophysically or biochemically and it would be futile to attempt this in the absence of appropriate facilities. But it would suffice to comment on the relationship between bacterial infection and crisis from the bacteriological, haematological and clinical evidence of presence of infection in these children in the absence of other known causes as dehydration, malarial infestation and other forms of stress.

The yield of positive blood cultures and other cultures in this hospital is relatively low. It is reported as 60-80% according to the annual returns of the Department of microbiology. This influences the results of this study directly; as 45% of the patients were bacteriologically positive. Another factor which accounts for the low positivity of the cultures is the widespread use of antibiotics in the surrounding health centres for minor ailments before seeking treatment at this Referral hospital. Although an attempt was made to exclude all children who had some form of antibiotic therapy before admission, there is no guarantee as to how genuine the parents were in answering to the author's question on this. There is usually a tendency of parents to withhold this kind of information from hospital personnel for reasons that are not very clear.
Bacterial infections are a leading cause for hospitalisation of patients with sickle cell disease especially in the developing countries (14), when malaria is excluded. Of the 40 patients in this study 18 had bacteriological positive cultures and the remaining 22 were negative on various cultures nevertheless had clinical and haematological evidence of presence of bacterial infection and indeed in those with pneumonia and osteomyelitis radiological findings were consistent with pyogenic infection. Further evidence of bacterial infection is shown by remarkable improvement of all these patients when antibiotics were given. This is in keeping with studies elsewhere (2, 3, 36). Buchanan et al. Studied leucocyte counts in children with sickle cell disease both in steady state and in crisis with bacterial infections and he found that the absolute polymorphonuclear leucocyte counts were more than 10,000 per cu mm in those with bacterial infection and this has been the finding in this study too, in which the average count was 11310 per cu mm. Although no band or stab counts were done in this study, the therapeutic response plus the absolute polymorphonuclear leucocytosis of more than 10,000 per cu mm highly suggest pyogenic infection in these culture negative patients.

The commonest reason for hospitalisation in this study was pneumonia and pharyngotonsillitis and the commonest organisms isolated were streptococcus pneumonia and staphylococcus aureus which were equally prevalent. Barret Connor (22) found that the streptococcus pneumonia was the single most common organism isolated in these patients and that pneumonia was the commonest reason for hospitalisation for children with sickle cell disease.
This has also been found by many other workers (23, 37).

The distinction between pulmonary infarction and pneumonia is radiologically difficult but clinically and by haematological indices this can easily be made especially when coupled with antibiotic response of the radiological changes in patients with pneumonia, (11, 15, 48).

Osteomyelitis is another common reason for hospitalisation for patients with sickle cell disease and salmonella osteomyelitis occurs with increased frequency when compared to normal population. Workers elsewhere have found salmonella organisms being the commonest causative organism for osteomyelitis in children with sickle cell disease (22, 24, 25). In this study there was no case of salmonella osteomyelitis but salmonella typhimurium was isolated in three patients with septicaemia and pneumonia. The three cases with osteomyelitis in this study were due to staphylococcus aureus (2 cases) and streptococcus pneumonia (1 case) which is consistent with findings in the normal population. However it's a known fact that even among sickle cell disease patients staphylococcus aureus and streptococcus pneumonia are the commonest organisms but the frequency of salmonella osteomyelitis is comparatively higher than in the general population. (49)

Meningitis was found in three of the patients in this study. It has been found to be relatively common in other studies. Robinson et al (39) found that the pneumococcus was responsible for 87% of all the meningitis cases in his study among sicklers and the remaining were due to staphylococcus aureus and Haemophilus influenza. In this study the pneumococcus was responsible for
two of the three cases and the third case was due to klebsiella. These patients all had concurrent pneumonia and same organisms were isolated from the blood. However only small numbers of meningitis are found in most studies. (26, 39, 50) It should however be noted that the pneumococcus is relatively rare at the age below 2 years but Robinson found the contrary in children with sickle disease. The two cases in this study with pneumococcal meningitis were in the 4 - 6 year age group.

The question of prophylactic antibiotics especially penicillins (long acting) as is the case with antimalarials cannot easily be answered from this study since pneumococcus was responsible for 5 out of the 18 cases (27.8%). From this therefore prophylactic penicillin would not be justified and the use of appropriate antibiotics based on culture and sensitivity would be ideal. However a study carried out in Mulago Hospital Kampala (20) showed that these patients under 6 years of age followed for 10 months or longer on both long acting penicillin and chloroquine prophylactically, had a significant low rate of dactylitis and a higher average haemoglobin level than those patients on placebo. However the role of the long acting penicillin is not yet clear since some organisms are not sensitive to penicillin but further work on this subjects is needed.

The majority of patients in this study were below 6 years of age accounting for 67.5% of all the patients. Most of these patients were however 4 - 6 years old (42.5%). This is unlike other studies (33) where most cases are reported to be under 2 years. This is not the case in this study probably because most of the children die within the first two years and what we are seeing are the survivors of whom a few may live upto adolescence and adulthood.
Thrombotic crisis was found to be the most common crisis accounting for 60% of the patients and was the commonest crisis in all age groups. This was followed by the mixed crisis, haemolytic and lastly the aplastic crisis. No case of sequestration crisis was encountered in this study whether this is because of its rarity or because they usually succumb before they arrive to hospital is not easy to say. This pattern was also seen when only the 18 positive cases were considered separately.

In this study respiratory infections accounted for 50% of the patients and of these 60% were found to be bacteriologically positive. Respiratory infections accounted for 66.7% (12 cases) of the 18 bacteriologically positive cases.

From all this we can deduce that infection probably has a part to play in the initiation of crisis in patients with sickle cell disease and that there must be immunological derangements in these patients. Bacteria are usually prevented from invading the body by a normal integument. When this system fails bacteria are introduced into the blood stream where they are taken up partly into the Reticuloendothelial system (liver and spleen) and phagocytes in the capillaries of the various organs especially the lungs. The organism may multiply in these loci leading to a bacteremia. Once the phagocytes have ingested the bacteria antigens are passed along the Reticuloendothelial system which recognises the antigens as foreign and initiate the production of antibody. The bactericidal activity of serum against gram negative organisms depends on antibody, complement and lysozymes. While these are bactericidal factors in serum too for gram positive organisms, the main factors are phagocytosis in the
presence of opsonins (specific antibody, complement and other heat labile factors).

Evidence for defective integument as a major disease mechanism in the bacterial infection of sickle cell anaemia is lacking. It has been proposed that the increased susceptibility to Salmonella septicaemia results from pathology secondary to sickling in the gastrointestinal tract but this has never been demonstrated (24). There is normal gastric secretion which is responsible for enteric organism defense (28). Patients with sickle cell disease have an overload of Kupfer cells with red blood cells breakdown products as well as increased incidence of cirrhosis and this is important in some patients with bacteraemia. The liver acts as a filter for bacteria. The spleen is important in host defences. It provides an anatomical site for bacteria as well as a slow sinusoidal circulation through a bed of macrophages capable of clearing bacteria. In young patients with sickle cell disease the spleen is usually large as a consequence of erythrophagocytosis and trapping of sickled cells. Later in life the spleen is virtually destroyed by repeated infarcts and fibrosis and thus absent or reduced splenic clearance occurs and thus becomes an inactive biological filter for particles (33).

Laboratory evidence of impaired splenic function in haemolysis reviewed by Kay, Gill and Hook in 1967 in a study in mice demonstrated increased susceptibility to Salmonellae in haemolysis with or without anaemia (25).
They concluded that erythrophagocytosis by Reticuloendothelial system interferes with capacity of the cells to kill bacteria. This is supported by increased incidence of salmonellosis in other states where there is chronic haemolysis (malaria, bartonellosis) and in other conditions involving the Reticuloendothelial system (schistosomiasis, lymphoma, Gaucher's disease). (51, 52, 53, 54).

However, splenectomised children have increased susceptibility to the pneumococcus especially when they are under 4 years of age. Pyogenic organisms (Pneumococcus, B-haemophilus influenza) usually invade through the respiratory tract. Initial defences occur without antibody by surface phagocytosis (27).

When despite this mechanism, the blood barrier is penetrated, pneumococci may be phagocytosed by polymorphonuclear leucocytes lining the blood vessels of the lungs and the Reticuloendothelial system by surface phagocytosis (again without antibody), and later by enhanced phagocytosis in the presence of opsonins.

In patients with sickle cell anaemia subclinical pulmonary thrombi, fluid filled alveoli and congestion could afford an excellent focus for bacterial multiplication and at the same time impair surface phagocytosis. Further phagocytosis by alveolar macrophages is impaired at reduced oxygen tension, patients with sickle cell anaemia have intrapulmonary shunting and reduced arterial $pO_2$ (29). In addition Winkelstein and Drachman have demonstrated deficient heat labile serum opsonizing activity for the pneumococcus but not for Salmonella in the serum of 12 of the 14 children with sickle cell anaemia (12) in their study. Thus it would appear that multiple...
factors favour the development of pneumococcal infection in sickle cell anaemia. Since more than one host defense factor is impaired in this population one could anticipate increased susceptibility to other bacteria in addition to pneumococcus and salmonella. This possibility was suggested by the data of Eecke et al (30) and supported by Barret-Connor (22). With age most susceptibles are either removed from the population or other defence mechanisms replace the known defects in bacterial immunity.

These observations do not explain the marked difference in susceptibility within the populations of patients with sickle cell anaemia. No other abnormalities of bacterial immunity have been demonstrated. Patients with sickle cell anaemia have levels of haemolytic complement serum immunoglobulins and antibody response to Salmonellae vaccines comparable with normal persons (26, 31, 32).
CONCLUSIONS:

1. Bacterial infection is a common cause of hospitalisation of patients with sickle cell disease. 45% of the cases in this study were positive on culture and the remaining had ample clinical, radiological and "therapeutic response" as evidence for bacterial infection.

2. 68% of the cases were under 6 years of age and the greatest risk of life threatening bacterial infection was common in these patients and 73% of the 13 positive cases were under 6 years of age. Gram positive bacteria were more prevalent (66.6%) than gram negative organisms. The commonest organisms were streptococcus pneumonia and staphylococcus aureus which were equal in occurrence.

3. The commonest reason for hospitalisation of the 40 patients was respiratory infections (pneumonia and pharyngotonsillitis) accounting for 20 of the 40 cases. Clinical pneumonia was not difficult to differentiate from pulmonary embolism on clinical, radiological and haematological findings together with a remarkable response to therapy of these patients to antibiotics clinically and radiologically.

4. 10% of the cases were found to have osteomyelitis but none of these cases were due to Salmonella species. Staphylococcus aureus and pneumococcus were causative in 50% and 25% respectively of the 4 cases, one case was negative on culture. Salmonella typhimurium was however responsible for 3 of the cases who presented as septicemia.

5. Although no definite causal relationship has been clearly shown in this study but the fact that 45% were positive on cultures and the presence of clinical, radiological and haematological features suggestive of pyogenic infection is corroborative evidence of bacterial infection as the possible precipitating factor in the causation of the crises (in the absence of clinical malaria). However biochemical studies on the Red blood cell are necessary to establish the role of bacterial infections in causation of crisis.
6. Thrombotic crisis is the commonest type of crisis. 24 of the 40 patients were in this crisis 13 of which were positive on bacterial cultures. No case of sequestration crisis was found.

7. As would be expected in this country 90% of the patients were the Luo and Lukhya ethnic groups who occupy the Nyarua and Western Provinces of Kenya.

8. The total mean absolute white cell count was over 17,000/cu mm (average) for the 40 patients with an average mean polymorphonuclear leucocyte count of more than 64% in the majority of the cases. The absolute mean polymorphonuclear leucocyte count was 11,310/cu mm (average) which is highly suggestive of presence of pyogenic infection in these patients including those who were culture negative.

RECOMMENDATIONS:

1. More research is required in the field of bacterial infections in patients with sickle cell disease especially in this country in reference to:

   (a) incidence of various bacterial organisms and malaria in patients with sickle cell disease.

   (b) a controlled study on the haematological parameters in patients with sickle cell disease both in stable state and in crisis due to whatever cause, especially for bacterial induced crisis.

   (c) A similar study to the one undertaken here by carried out in one of the hospitals in western Kenya involving a large number of patients with a control if possible.

2. There is ample evidence to indicate greater susceptibility
of patients with sickle cell disease particularly to pneumococcal and salmonella infections. A controlled study is necessary to establish what roles prophylactic penicillin (long acting) would play in reducing bacterial induced crisis and improving the haemoglobin level in these patients. This type of prophylaxis is already being given for malaria using paludrine or chloroquine.

3. All patients of the Luo and Lukhya ethnic groups should have a sickling test and haemoglobin electrophoresis carried out when they present to hospital with anaemia and bacterial infection before they are transfused especially in infants and younger children.

4. Genetic counselling should be attempted for all parents of children with sickle cell disease and for all sickle cell disease adolescents especially regarding marriage and child bearing.

5. The levels of G6PD should be estimated in children with sickle cell disease especially those in haemolytic crisis.

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PROFORMA

BACTERIAL INFECTIONS AND SICKLE CELL DISEASE

Date .......................... I.P. No. ........................

Name of patient ............................

Sex: .......................... Age .......................... Tribe ............................

Type of crisis: ............................

Clinical diagnosis: ............................

RESULTS:

1. Haemoglobin Electrophoresis:

2. Haemogram - Hb:
   - WBC Count
   - Differential
   - ESR
   - Reticulocyte Count:

3. Blood cultures:

4. Urine cultures:

5. Stool cultures:

6. Throat Swab cultures:

7. Radiological findings - Chest X-ray
   - Others