THE PATTERN OF INFECTIONS IN CHILDREN WITH HAEMATOLOGICAL MALIGNANCIES UNDERGOING TREATMENT AT KENYATTA NATIONAL HOSPITAL.

IN MEMORY OF

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THE PATTERN OF INFECTIONS IN CHILDREN WITH HAEMATOLOGICAL MALIGNANCIES UNDERGOING TREATMENT AT KENYATTA NATIONAL HOSPITAL.

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THE PATTERN OF INFECTIONS IN CHILDREN
WITH HAEMATOLOGICAL MALIGNANCIES UNDERGOING TREATMENT
AT KENYATTA NATIONAL HOSPITAL

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

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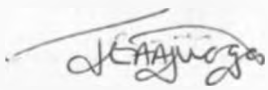

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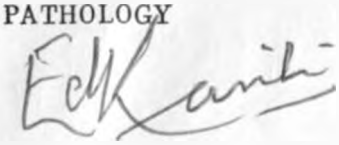


CONTENTS

SUMMARY:

During a 9 month period, 106 consecutive episodes of fever in 50 children with haematological malignancies were prospectively evaluated. The distribution of the haematologic malignancies were as follows: 17 cases had acute lymphocytic leukaemia; 18 malignant lymphoma (8 Hodgkin's , 8 Burkitt's and 2 lymphocytic lymphoma); 3 chronic granulocytic leukaemia and 12 acute non-lymphocytic leukaemia.

The common clinical diagnoses associated with febrile episode and positive isolates included septicemia (17 cases) pneumonia (11 cases), oral infections (11 cases) suppurative cutaneous lesions (7 cases) pharyngitis (9 cases) perianal infections (4 cases) and typhoid (3 cases).

62.3% of the episodes were aetiologically documented by bacterial isolates. Crystaline pencillin, Gentamicin and Co-trimoxazole were the most commonly employed antibiotics. Of the 80 bacterial isolates the most common were Staphylococcus aureus (28.8%) Klebsiella (20%), Streptococcus faecalis (15%) Staphylococcus albus (12.5%) and Escherichia coli (11.3%) There was one case of systemic candidiasis. Other isolates unrelated to fever were tinea (5 cases) and incidental findings of Hookworm and Trichuris trichuria in two specimens of stool. Viral infections diagnosed clinically included 4 cases of varicella, 2 of measles, 1 herpes labialis and 2 hepatitis.

The mortality in this series was 52% (80% of those admitted in relapse had a fatal outcome). 61.5% of the deaths were due to infections.

It may therefore be concluded from this study that in children with haematological malignancies (1) infection is a frequent cause of mortality (2) the most common cause of febrile

episodes is bacterial infection (3) Staphylococcus aureus, Klebsiella, Escherichia coli and Streptococcus faecalis are the most frequent bacterial isolates and Pseudomonas is infrequent. (4) viral infections are relatively frequent in this group of children and (5) with adequate management the mortality can be reduced.

OBJECTIVE

To conduct a prospective study to determine the incidence and aetiology of infections in children with haematological malignancies.

INTRODUCTION

There have been major advances in the management of malignant diseases in recent years, such that survival can be prolonged for most patients and cures may be anticipated for some (1,2,3) Among the reasons for this improving prognosis are advances in the management of infections both by prevention and therapy, allowing certain patients who would otherwise have died of these complications to survive long enough for effective cancer chemotherapy to be administered. (1,4,5,6,7).

Infection still remains the leading cause of both morbidity and mortality in children with haematological malignancies. (8,9, 10,11) Since many of the common bacterial infections can now be treated successfully, newer cancer chemotherapeutic regimens have led to an increasingly profound alteration in host defence mechanisms. These compromised defences, longer survival and the extensive use of antibiotics have encouraged the appearance of infections caused by organisms only rarely seen previously (8,9,12,13,14,15,16). Such infections have often proven difficult to diagnose and equally difficult to manage (10).

A review of the medical literature discloses a large volume of medical literature which deals both with the invading pathogen and the management of the infectious conditions in the immuno-depressed child. Some of the micro-organisms listed in the literature are only occasionally encountered in common practice (17,18,19,20).

The aetiology of clinically recognized infections in the compromised host has undergone considerable change in the last twenty years. Previously, Staphylococcus aureus was the major cause of severe infections, but by the late sixties Gram-negati organisms, especially Pseudomonas aeruginosa, became the most frequently isolated pathogens and remain so presently (21,22).

However, Staphylococcus aureus is still a major isolate in other studies (23,24,25,26).

In most recent studies at various centres Gram-negative bacteri have ranked first as causes of septicaemia in cancer patients. Among 34 cases of non-fatal sepsis in patients with leukaemia, Levine and colleagues (22) found only 4 cases of Gram-positive bacteraemia and in 3 the organism was Staphylococcus. Bodey and Rodriguez (27) encountered only 3 cases of Gram-positive bacteraemia among 54 episodes of severe infection in cancer patients receiving prophylaxis with antibiotics and kept in a protected environment. In a study of 414 patients with acute leukaemia, Hersh and associates (9) found that 14.7% of episode of septicaemia were due to Staphylococcus aureus. Singer, Kaplan and Armstrong (20) reported 9.4% of septicaemia episodes to be due to Staphylococcus aureus in the same type of patients

DeClerck and Rivard (26) reported equal proportions of Gram-positive and Gram-negative bacterial infections but the fatalit were greater with Gram-negative infections.

Kaplowitz (25) in his study of 113 admissions of children with leukaemia and lymphoma showed that Staphylococcus aureus, Escherichia coli and Klebsiella were most frequent isolates and were seen in about equal frequency. While Pseudomonas aeruginos the most common organism in other studies was isolated from only two out of 37 isolates in the study of Chilcote and Boehner (21).

A study in Argentina on 102 consecutive episodes of infection ir children with malignant disease by Lopez and Fernandezperona (23) showed that out of 75 bacterial isolates 55% were Gram-positive micro-organisms and 45% Gram-negative bacteria. Only three pathogens (Staphylococcus aureus, Streptococcus pyogenes and Escherichia coli) accounted for 55% of isolates.

Ladisch and Pizzo (24) reviewed the medical records of all patients of the Paediatric Oncology Branch of the National Cancer Institute who had a documented episode of Staphylococcus aureus sepsis over a nine year period (1968-1976). Seventy episodes of Staphylococcal sepsis occurred in 63 patients of a total population of approximately 500 new patients (77% acute leukaemia).

In another recent review by Miser (28), 101 consecutive episode of blood-culture positive infections were evaluated and the organisms most commonly causing blood culture positive infection in children with malignancy were found to be Staphylococcus aureus and Escherichia coli and that infection due to Gram-positive organisms, particularly Staphylococcus aureus was less frequently fatal.

As far as the bacterial infections are concerned in most centres, the gram-negative enteric bacilli (especially Klebsiella, Escherichia coli, Pseudomonas aeruginosa) represent the major pathogens in cancer patients. Infections due to Gram-positive bacteria (especially Staphylococci and Streptococci) very in their frequency, but in some institutions have surpassed Gram-negative organisms as the most frequent aerobic bacterial isolates. Serious infections with Group A Streptococcal infections are rare but are important in splenectomized patients.

Septicaemias with diphtheroids (especially Corynebacterium equi) (29) have been described and these infections are resistant to virtually all antimicrobials except vancomycin.

Anaerobic bacteria (Bacteroids, Clostridium, Fusobacteria and anaerobic cocci) infections are rare and infrequently observed (18,19,20,23,30). Nocardia (N. asteroides and N. brasiliensis) can cause serious infections in these patients. Lungs, brain and skin are the major sites of infection (19,20,22,30).

Myobacterium infections in these children do not seem to be increased (30) compared with other children in the population. Fungal infections have now become increasingly recognized as a cause of morbidity and mortality in children with haematological malignancies. Candida, Aspergillus, Mucor, Cryptococcus and Histoplasma are the organisms most frequently responsible. (9,12,17,19,20,22,23,30,31). Protozoan infections are usually due to the reactivation of latent organisms as in Pneumocystis carinii and Toxoplasma gondi. (12,23,30,31,32,33).

The spectrum and severity of viral infections in these patients is wide and depends on age, prior exposure, immune response to the specific viral infection, as well as the underlying disease and the exposure to chemotherapy and radiotherapy. Morbidity in these patients is mostly encountered with the Herpes virus as the cell-mediated immunity is more defective. Some of the viral infections may lead to secondary bacterial infection. The human Herpes viruses (Herpes simplex I and II, Varicella-Zoster, Cytomegalovirus and Epstein-Barr virus) are ubiquitious in nature and can cause both primary infection (herpes stomatitis, chicken-pox and mononucleosis syndromes) or can become latent and result in reactivation infections (gingivostomatitis, shingles) (34,35,36). Other virus of importance in causing infections are Hepatitis, Measles and Influenza. Vaccinia, Mumps, Rubella and Polio viruses do not appear to have increased morbidity in these patients (37,38).

Inspite of the extensive information available from other countries and institutions neither the true local incidence of pathogens nor the morbidity - mortality of children with haematological malignancy with infections have been carried out in Kenya. Most children with haematological malignancies are treated in Paediatric wards at Kenyatta National Hospital and are placed on chemotherapy according to the regimens designed by Kasili (39,40).

MATERIALS AND METHODS

A prospective study was done on children under 14 years of age with haematological malignancies admitted to the Paediatric wards at the Kenyatta National Hospital between December 1, 1981 and August 31, 1982. All the children that were included in the study had the diagnosis confirmed by a bone marrow or lymph node biopsy, where necessary. Other initial diagnostic and staging work-up included: A full blood count, cytochemistry (where applicable), urea and electrolytes, liver function tests, stool for ova/cysts and culture, urinalysis, chest X-ray, intravenous urogram and lumber puncture where necessary. All the findings were recorded in a performa (Appendix I) The criteria for inclusion in the study were that in addition to the malignant condition, the patient had either a temperature in excess of 37.5°C for more than 24 hours or an obvious sign of infection. Children on blood transfusion or anti-neoplastic infusion therapy who spiked a temperature were investigated for the cause but were excluded from the analysis.

All the patients in the study had daily thorough physical examination by the investigator to detect any infective complications. When patients had a temperature in excess of 37.5°C for more than 24 hours or an obvious sign of infection, specimens for culture from blood, throat, urine, stool and any other appropriate sites were collected and delivered to the Microbiology Department at Kenyatta National Hospital. Blood for a full blood count including differential white blood count platelet count, and blood film were also taken and delivered to the Haematology Department at KNH. All the specimens were take before institution of antibiotic therapy.

The initial antibiotic therapy for presumed infection were Crystalline penicillin and Gentamicin administered intravenousl All the findings and investigations done were recorded in the performa (Appendix II and III).

In twenty five children with haematological malignancies specimen for blood, throat, urine and stool cultures were taken as a baseline before institution of chemotherapy irrespective of whether they had fever or other signs of infection.

Forty children in the same wards who had neither haematological malignancies nor immuno-suppression but were suffering from different illnesses for which they were on treatment were investigated if they had a temprature in excess of $37.5^{0}C$ for more than 24 hours or signs of infection. They were a comparison group for the study group which were immuno-suppressed and were on chemotherapy.

Consent for the study was obtained from the research ethical committee and an informed consent was obtained from the parents of the children.

INVESTIGATIONS

Blood culture

A blood specimen of 6 c.c was drawn by venepuncture; the skin of the patients arm at the antecubital fossa or dorsum of the hand was disinfected by applying 70% spirit. A tourniquet was applied round the upper arm about the middle of the biceps to render the veins turgid. The needle of the syringe was inserted into a prominent vein and blood drawn. The tourniquet was then released. The needle was withdrawn from the vein. The patients arm was raised after blood had been withdrawn and firm pressure applied to the site of the puncture to obviate haematoma formation.

Three blood culture bottles were used: Two containing 5 c.c. of brain infusion both in aerobic media and one containing 5 c.c. of sodium thioglycollate broth in anaerobic media. The needle of the syringe containing the withdrawn blood was immediately passed through each rubber washer to expel about 2 c.c. of blood into each bottle containing media. The specimens were then taken to the laboratory and incubated in the upright

position at 37°C for 24 hours. For aerobic media subculture on MacConkey and Chocolate blood agar was done. MacConkey agar was incubated at 37°C overnight aerobically while Chocolate blood agar was put in carbondioxide jar and incubated at 37°C overnight. After 18-24 hours of incubation the culture were examined for growth and species identification and antibiotic sensitivity. A second subculture was done in the same way as above and read the following day. The blood culture for anaerobic media was treated in the same way as above but on second subculture, sheep blood agar was included and the three plates were incubated at 37°C anaerobically using gas-pack jars. The blood culture bottles were kept for 3 weeks at 37°C and subcultured at weekly intervals. At the end of three weeks if no growth was obtained they were discarded as negative

The antibiotic sensitivity was done by using Oxoid Multodisks. For Gram-negative organisms discs containing following concentrations were used.

Ampicillin	25 mcg	Tetracycline	25 mcg
Co-trimoxazole	25 mcg	Gentamicin	10 mcg
Streptomycin	10 mcg	Sulphonamide	200 mcg
Kanamycin	30 mcg	Chloramphenicol	30 mcg

For the Gram-positive organisms discs containing following concentrations were used:

Penicillin G	1 unit	Co-trimoxazole	25 mcg
Minocycline	30 mcg	Chloramphenicol	30 mcg
Erythromycin	15 mcg	Ampicillin	10 mcg
Methicillin	5 mcg	Lincomycin	2 mcg

Urine culture

A mid-stream urine specimen was collected into a sterile bottle after the vulva or glans penis was cleaned with tap water. In older girls the labia are separated by the patient or nurse and the vulva cleaned twice in an anteroposterior direction

with swabs soaked in tap water and then finally with a dry swab. Whilst the labia are still held a part some urine, 20-50 ml, was passed into a bowl, but the next portion (midstream urine) was collected into a sterile bottle.

Where it was difficult or in the younger children the external genitalia was cleansed and a specially designed adhesive plastic bag attached covering the urethral opening. The specimen was then taken to the Microbiology Laboratory within an hour. Microscopical examination was carried out using "well slides" and viewed for red blood cells, white blood cells, pus cells, casts, epithelial cells, Trichomonas and ova of schistosoma. Urinalysis by "Combur 8" test strips (Mannheim Boehringer) tested for Nitrite, PH, protein, glucose, Ketones, urobilinogen, bilirubin and blood.

Cultures were performed by inserting a 0.001 ml wire loop sterilized by flaming first into the specimen and plating onto cystein lactose electrolyte deficient medium (CLED). The culture was incubated at 37°C and examined after 24 hours for growth, colony count and species indentification and antibiotic sensitivity. The antibiotic sensitivity was done by using Oxoid Multodisks containing the following concetration.

Ampicillin	25 mcg	Streptomycin	25 mcg
Tetracycline	100 mcg	Sulphonamide	200 mcg
Nitrofurantoin	200 mcg	Gentamicin	10 mcg
Nalidixic acid	30 mcg	Co-trimoxazole	25 mcg

Stool culture

Fresh stools were collected in a clean plastic container and sent to the Microbiology laboratory for microscopy and culture. Stools were cultured by direct plating a deoxycholate citrate agar (DCA) and inoculation into selenite-F-broth. After overnight incubation at 37°C the broth was subcultured on DCA. The cultures were then examined for

growth and non-lactose fermenters were inoculted into urea for 2 hours. If they were urea negative, then broth was inoculated on Triple Sugar Iron Agar (TSI) and incubated at 37°C overnight and read after 18-24 hours. Salmonella and Shigella were identified by sugar reaction in TSI, Salmonella typing was carried out by slide agglutination using specific antisera by following Kauffmann White scheme 1961 to identify the species. For Shigella identification specific antisera (Edwards and Ewing 1972) were used. For enteropathogenic Escherichia coli in children the lactose fermenters were inoculated on DCA and identification of serotypes was by use of commercially prepared antisera.

For ova and cysts the formol-ether concentration method was used. Microscopy was done to detect any ova or cysts directly and by use of Lugol's Iodine.

Throat culture

The fauces were swabbed using the serum swab and taken to the Microbiology laboratory within one hour. The swab was streaked on MacConkey sheep blood agar and Chocolate agar. MacConkey and sheep blood agar, containing optorchin disc were incubated at 37°C aerobically and Chocolate agar in carbon-dioxide overnight in an extraction jar. The following day the cultures were examined for growth, species identification and antibiotic sensitivity as above.

Other tests included purulent materials from skin, mucous lesions, eyes or subcutanous tissue and specimens sent to the laboratory for culture and sensitivity as above.

Fungal culture

Scrapings from superficial lesions on the body were obtained an put in 30% potassium hydroxide and left for one hour. The

direct microscopy was done to detect any fungal elements i.e. hyphae, spores or yeasts. If the microscopy was positive then culture was done on Sabouraud's media (containing either actidione, chloramphenicol, streptomycin or penicillin to inhibit bacterial growth) and incubated at 22°C and 37°C for one week. The growth was then observed for species identification. Wet preparations were made with lacto-phernol-blue to identify the mycelia, microconidia and macroconidia.

Where there was a clinical suspicion of meningitis a lumber puncture was done and CSF sent for microscopy and culture/sensitivity and sugar and proteins.

Viral infections included in the study were clinically diagnosed without laboratory investigations.

Haematological tests

2 ml sample of venous blood was collected into a sequestrene bottle for the following tests:

a. Full blood count, using the Coulter Counter Model 'S'
b. A peripheral blood film stained by May-Grunwald Giemsa was reported and a differential white cell count done.
c. Malarial parasites or pigments were looked for.

Catergorization of infections

Criteria for categorization of infection were as follows:

Septicemia - one single positive blood culture with a significant pathogen.

Pneumonia - patient with fever, cough, respiratory distress, physical signs of crepitations or of consolidation, chest X-ray evidence of pulmonary infiltrate, with positive or negative blood cultures.

Osteomyelitis - patients with bone pain, tenderness on pressure swelling, purulent discharge, obtained by needle aspiration or

surgical draining, positive blood culture and radiological changes.

Otitis media inflammed ear drum with positive blood culture, or purulent discharge from ear.

Pharyngitis - pain on swallowing, inflammed throat, or purulent exudate on mucous membrane or tonsils with enlargement and lymphadenopathy.

Stomatitis - ulceration of oral mucosa.

R E S U L T S:

50 children with haematological malignancies were included in this 9 months prospective study of whom 25 were investigated pretreatment.

Acute lymphocytic leukaemia was the most frequent haematologic malignancy accounting for 17 cases (34% of total diagnosis) followed by 12 cases of acute non-lymphocytic leukaemia. Others were 8 cases each of Hodgkin's disease and Burkitt's lymphoma, 3 cases of chronic granulocytic leukaemia and 2 cases of lymphocytic lymphoma (Table 1). In this study there was a male preponderance of 32 males to 18 females. Male to female ratio of 1.8:1.

Figure 1 shows that the majority of the children fell in the age group between 5 to 9 years accounting for 24 (48%) cases. There were 14(28%) cases between 0 to 4 years and 12(24%) between 10 to 14 years. There was a male preponderance in 0 to 4 years and 5 to 9 years groups but in 10 to 14 years the female predominated.

Table 2 shows that most of the children with acute leukaemia were males (11 of 12 acute non-lymphocytic leukaemia and 11 of acute lymphocytic leukaemia) while 2 of 3 cases of chronic granulocytic leukaemia were females. Other malignancies were uniformly distributed between the two sexes.

On admission the study group children were in poor general condition. The mean haemoglobin value was 9.7g/dl. 21 were having haemoglobin levels between 6 to 8 g/dl and 3 under 6 g/dl.

The mean leuocyte count was 15.1 x 10^9/l. In 25 cases the leucocyte count was between 5-10 x 10^9/l and 4 cases had leucocyte count less than 5 x 10^9/l while 21 cases were more than 10 x 10^9/l. 9 cases were neutropenic on admission

(neutrophil count 0-0.5 x 10^9/1) 13 cases had moderate neutropenia 0.5-1.0 x 10^9/1 and 28 cases had over 1.0 x 10^9/1. Platelet count was less than 100 x 10^9/1 in 22 cases and over 100 x 10^9/1 in 28 cases (Table 3).

In the twenty five children with haematological malignancies who were investigated on admission as a pre-treatment group, 10 of them had a temperature more than 37.5°C. 6 had positive blood culture of which the organisms isolated were Klebsiella-2 and one each of Salmonella, Alcaligenes, Staphylococcus albus and Streptococcus faecalis. Two had positive throat swab cultures which grew Streptococcus faecalis (Table 4,5). On admission two of these patients had pharyngitis (Streptococcus faecalis -2) one had stomatitis (Staphylococcus albus) one typhoid (Salmonella two cases of pneumonia (Klebsiella) and two had septicaemias (Alcaligenes and Streptococcus faecalis). One child had a right cervical lymph node which was infected but all cultures were negative and in one other child all the cultures were negative and there were no signs of infection but the temperature was above 37.5°C (This patient might have had a viral infection or could be due to the malignant disease itself).

106 episodes of suspected infections were investigated, of which 66 were bacterial, 8 viral and one fungal.

In 31 cases no cause for the fever could be indentified but a clinical impression was made and were treated appropriately. Pneumonia -9, Otitis media -4, Stomatitis -2, Perianal abscess-2 Osteomylitis -2, Post-transfusion and chemotherapy -4, Febrile-8 and these may have been due to the malignant disease itself or viral infections .

Of the 106 blood culture done 35 were positive (33%), the commonest isolates being Staphylococcus albus and Klebsiella 9 each, Staphylococcus aureus 5, Streptococcus faecalis and Salmonella 3 each, Pseudomonas 2. Out ot the 106 throat swabs

done, only 9 were positive, the commonest isolates being Streptococcus faecalis 6, and one each of Staphylococcus aureus, Staphylococcus albus, Klebsiella, and Escherichia coli. Of the 106 urine cultures done, 4 proved positive Klebesiella 2, Escherichia coli 1 and one mixed growth of Klebsiella and Escherichia coli. Of 106 stool cultures done only one grew Shigella. Nine cultures out of 18 from oral lesions were positive and the isolates were as follows: Staphylococcus aureus 5; Streptococcus faecalis 2; Escherichia coli 1; and one grew Klebsiella and Staphylococcus aureus. Seven of the 10 skin lesion swab were positive and the isolates were as follows: Staphylococcus aureus 4, Klebsiella 1 and mixed growth of Staphylococcus aureus and Citrobacter 1, and Staphylococcus aureus and Escherichia coli 1. Four of the 6 suppurative lesions in the perianal region were positive and the isolates were as follows: Staphylococcus aureus 1, Escherichia coli 1, mixed growth of Staphylococcus aureus and Escherichia coli 1. Two of the 4 ear swabs done were positive and the isolates were as follows: Staphylococcus aureus 1 and mixed growth of Staphylococcus aureus and Klebsiella 1. One culture from an eye swab grew Staphylococcus aureus. (Table 7,8).

Hence out of the 80 bacterial isolates 45 were due to Gram-positive (56.3%) and 35 due to Gram negative (43.7%). Staphyloccus aureus occured in 28.8% followed by Klebsiella 20%, Streptococcus faecalis 15%, Staphylococcus albus 12.5% and Escherichia coli 11.3%.

Of the 12 skin scraping for fungal culture, 5 were positive and the isolates were as follows: Trichophyton and Microsporum ferugineum 2 cases each and one of Geotrichum candidum. One case with candidiasis grew Candida albicans from blood and sputum.

Clinically documented viral infection were as follows: 4 cases of Varicella occuring during induction. 3 of them were neutropenic and their outcome was fatal. There were 2 cases of Measles, one occuring at diagnosis and the other was fatal in a child in relapse of his disease who was also neutropenic. There was one case each of Herpes labialis and Hepatitis.

One case of severe scabies (Norwegian type) occured in a child with Hodgkin's disease during his 2nd course of therapy. It responded to treatment (Table 9).

There was an incidental finding of Hookworm and Trichuris trichura in two stool specimens.

The commonest clinical diagnosis were septicemia (17.6%), pneumonia (12.9%), Stomatitis (12.9%), pharyngitis (10.6%), skin ulcers (8.2%), perianal ulcers (4.7%), urinary tract infection (4.7%) and chiken-pox (4.7%). (Table 10)

Isolates from 17 episodes of Septicemia were Staphylococcus albus, Staphylococcus aureus 3, Klebsiella 2, Streptococcus faecalis 2 and one each of Escherichia coli, Acintobacter, Citrobacter, Alcaligenes, Alcaligenes and Pseudomonas.

8 of the 11 pneumonia were caused by Gram-negative and 3 by Gram-positive bacteria. The isolates were Klebsiella 7, Staphylococcus albus 2, Staphylococcus aureus 1 and Pseudomonas 1.

Positive isolates from the oral lesions were Staphylococcus aureus 6, Streptococcus faecalis 2, and one each of Escherichia coli, Klebsiella and Staphylococcus albus.

Common organisms isolated during episodes of pharyngitis were Streptococcus faecalis 6, Staphylococcus aureus 2 and one each of Staphylococcus albus, Escherichia coli and Klebsiella. Two cases had mixed positive cultures, One was Streptococcus faecalis and Staphylococcus albus and the other was Escherichia coli and Staphylococcus aureus.

Isolates from the superficial skin ulcers were Staphylococcus aureus 6, and one each of Citrobacter, Klebsiella and Escherichia coli.

Isolates from peri-anal ulcers were Escherichia coli 3, Staphylococcus 2 and Streptococcus faecalis 1.

Isolates from urinary tract infection were Klebsiella 3 and Escherichia coli 2.

There were 3 cases of typhoid and the blood culture grew Salmonella.

There was one case of Staphylococcus aureus conjunctivitis and one of Shigella dysentery.

One case of systemic candidiasis where Candida albicans was grown from sputum and blood. (Table 11)

Table 12 and 13 show results of culture and positive isolates from the non-immunosuppressed patients. Out of 30 bacterial isolates 14 were due to Gram positive (46.7%) and 16 due to Gram negative (53.2%). Common isolates were Staphylococcus aureus 16.7%, Streptococcus faecalis 16.7%, Escherichia coli 13.3%, Staphylococcus albus 10%, Klebsiella 10% and Salmonella 10%.

It can be seen that the organisms isolated in the non-immuno-suppressed group is different from the study group where Staphylococcus aureus occurred in 28.8% followed by Klebsiella 20% and Streptococcus faecalis 15%.

The sensitivity pattern of bacteria isolated in the study is shown in Table 15. Staphylococcus aureus was sensitive to Chloramphenicol and Methicillin in 96% of cases while they were completely resistant to penicillin and ampicillin. Staphylococcus albus showed 86% sensitivity to Methicillin but low sensitivity to Minocycline, co-trimoxazole, chloromphenicol, ampicillin and lincomycin, Streptococcus faecalis was sensitive to erythromycin and Chloramphenicol in 78% of cases. Hence there was generally very low sensitivity to penicillin in Gram-positive bacteria. For the Gram-negative organisms Kanamycin and Gentamicin showed high activity to most of them, especially Klebsiella and Escherichia coli. Pseudomonas had a low sensitivity to most antibiotics except Amikacin. Other drugs which had relatively good senstivity were Chloramphenicol and Streptomycin. Hence the drug of choice for Gram-negative is Kanamycin or gentamicin and for Gram-postive is Methicillin.

Out of the 50 children in this series 26 had a fatal outcome (mortality 52%). 80% of those admitted in relapse had a fatal outcome. 61.5% of the deaths were due to infections (Bacterial - 10, Viral 5 and Fungal 1). Other causes of death were haemorrhage 5 , non-responsive to chemotherapy 2 , intracranial haemorrhage 1 , disseminated intravascular coagulation 1 and Leukaemic skin infiltration 1 .

Table 1: Type and sex distribution of neoplasms studied

TYPE	SEX		TOTAL
	M	F	
AML	3	0	3
AP-ML	1	0	1
AMoL	2	0	2
AMMoL	5	1	6
ALL	6	2	8
ALSL	4	4	8
APLL	1	0	1
CGL	1	2	3
Hodgkin's disease	4	4	8
Lymphocytic lymphoma	1	1	2
Burkitt's lymphoma	5	3	8
Total	32	18	50

ABBREVIATIONS USED

AML	Acute Myeloblastic Leukaemia
AP-ML	Acute Promyelocytic Leukaemia
AMoL	Acute Monoblastic Leukaemia
AMMoL	Acute Myelomonocytic Leukaemia
ALL	Acute Lymphoblastic Leukaemia
ALSL	Acute Lymphosarcoma Cell Leukaemia
APLL	Acute Prolymphocytic Leukaemia
CGL	Chronic Granulocytic Leukaemia

Table 2: Type and age distribution of neoplasms studied

TYPE	AGE IN YEARS						TOTAL
	0 - 4		5 - 9		10 - 14		
	M	F	M	F	M	F	
AML	0	0	3	0	0	0	3
AP-ML	0	0	0	0	1	0	1
AMoL	1	0	1	0	0	0	2
AMMoL	2	0	3	0	0	1	6
ALL	5	0	1	1	0	1	8
ALSL	2	0	1	2	1	2	8
APLL	0	0	1	0	0	0	1
CGL	0	0	0	1	1	1	3
Hodgkin's disease	1	0	2	2	1	2	8
Lymphocytic lymphoma	0	0	1	1	0	0	2
Burkitt's lymphoma	1	2	4	0	0	1	8
Total	14		24		12		50

ABBREVIATIONS USED

AML	Acute Myeloblastic Leukaemia
AP-ML	Acute Promyelocytic Leukaemia
AMoL	Acute Monoblastic Leukaemia
AMMoL	Acute Myelomonocytic Leukaemia
ALL	Acute Lymphoblastic Leukaemia
ALSL	Acute Lymphosarcoma Cell Leukaemia
APLL	Acute Prolymphocytic Leukaemia
CGL	Chronic Granulocytic Leukaemia

Fig. 1 Age distribution of study group

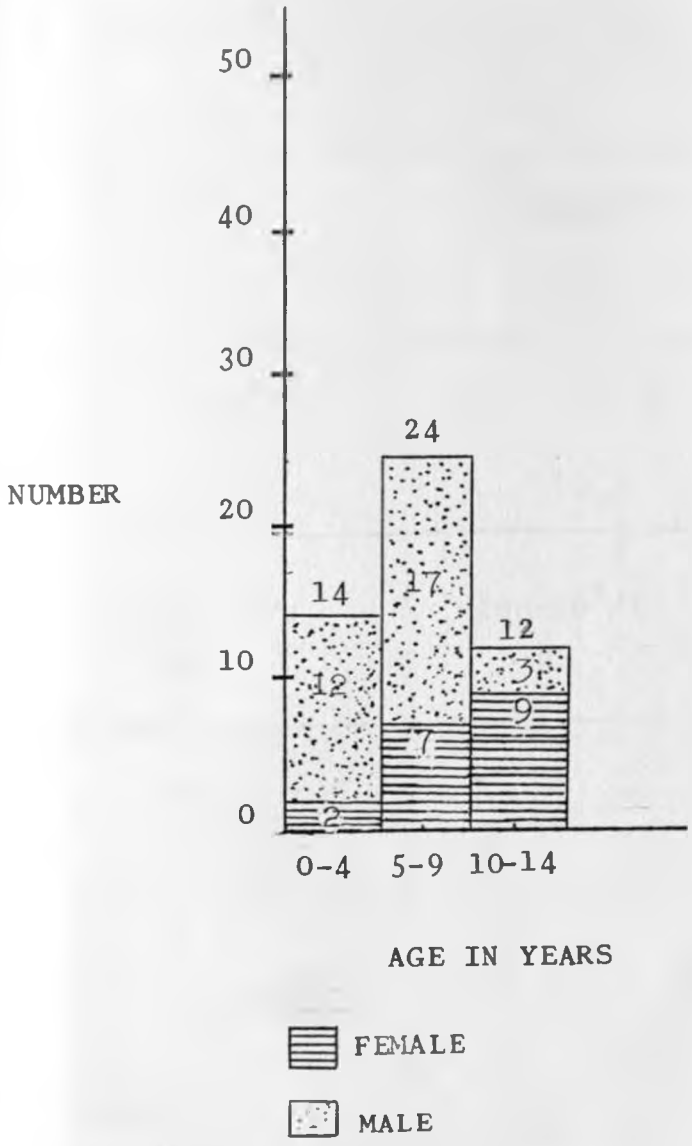


Table 3: Haematological parameters on admission

Hb MEAN 9.7g/dl	<6g/dl	6 - 8g/dl	>8g/dl
	3	21	26
WBC MEAN $15.1 \times 10^9/l$	$<5 \times 10^9/l$	$5 - 10 \times 10^9/l$	$>10 \times 10^9/l$
	4	25	21
Neutropil Count	$<0.5 \times 10^9/l$	$0.5-1 \times 10^9/l$	$>1 \times 10^9/l$
	9	13	28
Platelet	$<100 \times 10^9/l$	$>100 \times 10^9/l$	
	22	28	

Table 4: Pre-treatment specimen sampling in 25 patients on admissic

Culture specimen	Total numbers	Positive cultures	%
Blood	25	6	24
Throat swab	25	2	8
Urine	25	0	0
Stool	25	0	0

Table 5: Positive isolates from the pre-treatment samples

Organisms	Blood culture.	Throat cultures
Gram-positive		
Straphylococcus albus	1	0
Streptococcus faecalis	1	2
Gram-negative		
Klebsiella	2	0
Salmonella	1	0
Alcaligenes	1	0

Table 6: Distribution of positive isolates in relation to site of infection in pre-treatment patients.

	Aetiologic agent	Number
Pharyngitis	Streptococcus faecalis	2
Stomatitis	Staphylococcus albus	1
Septicemia	Alcaligenes	1
Septicemia	Streptococcus faecalis	1
Typhoid	Salmonella	1
Pneumonia	Klebsiella	2

Table 7: Type of specimen sampled for bacterial and fungal cultures in study group

Culture specimen	Total number	Positive cultures	
		number	%
Blood	106	35	33
Throat swab	106	8	7.5
Urine	106	4	3.8
Stool	106	1	0.9
Oral swab	18	9	50
Skin lesion swab	10	7	70
Perianal swab	6	4	66.7
Ear swab	4	2	50
Eye swab	2	1	50
Skin scraping for fungus	12	5	41.7
Sputum	6	1	6.3

Table 8: Positive bacterial isolates in relation to specimen sampled in the study group

	BLOOD CULTURE	THROAT CULTURE	URINE CULTURE	MUCO CUTANOUS	SKIN SWAB	ANAL ULCER	EAR SWAB	EYE SWAB	TOTAL NO	%
Gram-positive Bacteria										
Staphylococcus aureus	5	1	0	6	6	2	2	1	23	28.8
Staphylococcus albus	9	1	0	0	0	0	0	0	10	12.5
Streptococcus faecalis	3	6	0	2	0	1	0	0	12	15
Gram-negative Bacteria										
Klebsiella	9	1	3	1	1	0	1	0	16	20
Escherichia coli	1	1	2	1	1	3	0	0	9	11.3
Pseudomonas	2	0	0	0	0	0	0	0	2	2.5
Salmonella	3	0	0	0	0	0	0	0	3	3.8
Shigella (STOOL CULTURE 1)									1	1.2
Acientobacter	1	0	0	0	0	0	0	0	1	1.2
Citrobacter	1	0	0	0	1	0	0	0	2	2.5
Alcaligenes	1	0	0	0	0	0	0	0	1	1.2
									80	100

Table 9: The micro-organisms encountered in the study

	Number	%
BACTERIAL ISOLATES		
Gram-positive		
Staphylococcus aureus	23	51.1
Staphylococcus albus	10	22.2
Streptococcus faecalis	12	26.7
TOTAL	45	100
Gram-negative		
Klebsiella	16	45.7
Escherichia coli	9	25.7
Pseudomonas	2	5.7
Acientobacter	1	2.9
Salmonella	3	8.5
Citrobacter	2	5.7
Alcaligenes	1	2.9
Shigella dysenteriae	1	2.9
TOTAL	35	100
FUNGAL ISOLATES		
Candida albicans	1	
Trichophypon	2	
Microsporum ferrugineum	2	
Geotrichum candidum	1	
VIRAL (Clinical diagnosis)		
Measles	2	
Chicken-pox	4	
Herpes labialis	1	
Hepatitis (HB_sAg POSITIVE)	1	
SCABIES	1	

Table 10: Topographic distribution of infections

	Number of cases	%
Septicemia	17	17.6
Stomatitis	11	12.9
Pneumonia	11	12.9
Pharyngitis	9	10.6
Skin - ulcerations	7	8.2
- tinea	5	5.9
- anal ulcers	4	4.7
- scabies	1	0.9
Urinary tract infection	4	4.7
Varicella	4	4.7
Typhoid	3	3.5
Otitis media	2	1.8
Measles	2	1.8
Herpes labialis	1	0.9
Conjunctivitis	1	0.9
Dysentry	1	0.9
Hepatitis	1	0.9
Candidiasis	1	0.9
Hookworm	1	0.9
Trichuriasis	1	0.9
Total (Hookworm & Trichuriasis excluded)	85	100

Table 11: Distribution of positive isolates in relation to site of infection.

	Aetiologic agent	Number
Septicemia	Straphylococcus albus	7
	Staphylococcus aureus	3
	Klebsiella	2
	Streptococcus faecalis	2
	Escherichia coli	1
	Acintobacter	1
	Citrobacter	1
	Alcaligenes	1
	Pseudomonas	1
Stomatitis	Staphylococcus aureus	6
	Streptococcus faecalis	2
	Escherichia coli	1
	Klebsiella	1
	Staphylococcus albus	1
Pneumonia	Klebsiella	7
	Staphylococcus albus	2
	Staphylococcus aureus	1
	Pseudomonas	1
Pharyngitis	Streptococcus faecalis	6
	Staphylococcus aureus	2
	Staphylococcus albus	1
	Escherichia coli	1
	Klebsiella	1
Skin ulcers	Staphylococcus aureus	6
	Citrobacter	1
	Klebsiella	1
	Escherichia coli	1
Tinea	Trichophyton	2
	Microsporum ferrugineum	2
	Geotrichum candidum	1
Perianal infections	Escherichia coli	3
	Staphylococcus aureus	2
	Streptococcus faecalis	1
Urinary tract infection	Klebsiella	3
	Escherichia coli	2
Typhoid	Salmonella	3
Otitis media	Staphylococcus aureus	2
	Klebsiella	1
Conjunctivitis	Staphylococcus aureus	1
Gastrointestinal tract	Shigella dysenteriae	1

Table 12: Culture results from specimens sampled from the non-immunosuppressed group

Culture	Total number	Positive	%
Blood	40	17	42.5
Throat	40	0	0
Urine	40	5	12.5
Stool	40	1	2.5
C.S.F.	3	0	0
Skin-suppurative lesion	1	1	100
Ear	3	3	100
Sputum	1	1	100
Pleural Aspirate	1	0	0

Table 13: Positive bacterial isolates in the non-immunosuppressed group

	Blood culture	Urine culture	Stool culture	Ear swab	Skin swab	Sputum	No	%
Gram-positive Bacteria								
Staphylococcus aureus	3	0	-	1	1	-	5	16.7
Staphylococcus albus	3	0	-	-	-	-	3	10
Streptococcus faecalis	3	2	-	-	-	-	5	16.7
Streptococcus viridans	1	0	-	-	-	-	1	3.3
Gram-negative Bacteria								
Klebsiella	2	1	-	-	-	-	3	10
Escherichia coli	-	4	-	-	-	-	4	13.3
Pseudomonas	1	-	-	1	-	-	2	6.6
Salmonella	2	-	1	-	-	-	3	10
Citrobacter	2	-	-	-	-	-	2	6.6
Proteus	-	-	-	1	-	-	1	3.3
Acid-Fast Bacilli					-	1	1	3.3
							30	100

Table 14:

Sensitivity pattern

	Penicillin	Methicillin	Erythromycin	Minocycline	Co-trioxazole	Chloramphenicol	Ampicillin	Lincomycin	Tetracycline	Streptomycin	Kanamycin	Gentamicin	Sulphafurazole	Nitrofurantoin	Nalidixic acid	Pyopen	Polymyxin B	Amikacin
Staphylococcus aureus (26)	0	96	27	35	58	96	0	27										
Staphylococcus albus (7)	0	86	57	29	29	29	29	29										
Streptococcus faecalis (9)	11	67	78	11	11	78	89	56										
Klebsiells (14)					21	21	7		29	21	57	79	14	60	60			
Escherichia coli (8)					50	50	38		25	38	75	100	38	100	100			
Pseudomonas (2)					0	0	0		0	0	0	50	0	0	0		100	100
Salmonella (3)					100	100	67		67	0	100	67	0					
Shigella (1)					100	100	100		100	100	100	100	100					
Acientobacter (1)					100	100	100		100	100	100	100	100					
Citrobacter (2)					50	50	50		50	50	100	100	0					
Alcaligenes (1)					0	0	0		0	0	0	0	0			100	0	0

DISCUSSION

General overview

Infection remains a major cause of death in the patient with haematologic malignancies primarily as a consequence of the profound alterations of normal host defences which result from the malignancy, its treatment, or both (8,9,10,11). The impaired host defenses which occur in these patient, and the interaction of these defects with the endogenous and exogenous microbial flora is essential for early recognition, effective treatment, and prevention of serious infectious complications are to be accomplished The biology and pathophysiology of the compromised host is important as it shows how vulnerable to infection these children are.

The skin and the mucosal surfaces constitute the primary defence of the host against invasion by endogenous and acquired micro-organisms. The integrity of this physical barrier can be disrupted by the tumour (e.g. local invasion or obstruction) or by its treatment (surgery, intravenous injections, radiation, and chemotherapy - induced dermatitis or mucositis). These lesions provide a nidus for microbial colonization, a focus for local infection, and a portal for systemic invasion.

The neutrophil and the macrophage are the major cellular defences against most bacteria and fungi. Whether disease related or a consequence of therapy, the degree and duration of granulocytopenia is inversly related to risk of serious infection. In addition to quantitative defects qualitative abnormalities of neutrophil function have been described in cancer patients. These include defects in chemotaxis, phagocytosis and bactericidal capacity (41). Cancer chemotherapy may also produce defects of neutrophil function. Corticoteroids can decrease phagocytosis and neutrophil migration (42). The combination of prednisone with vincristine, 6-mercapto-purine and methotrexate has been shown to produce a significant decrease in the phagocytic and killing capability of leucocytes (43).

Bacteriocidal activity may also be transiently impaired within the three months following craniospinal irradiation in patients with leukaemia, (44) and may thus contribute to the infectious complications which may occur.

The macrophage-monocyte system provides residual phagocytic capacity during peroids of severe neutropenia, since the mature macrophage is more resistant to cytotoxic chemotherapy than the granulocyte. The activated macrophage is also associated with T-lymphocytes as an effector of cell-mediated immunity and is an important defence against mycobacteria, Listeria, Brucella, and several fungi protozoans and viruses.

Patients with lymphoma (especially Hodgkin's disease) have significant alterations of cell-mediated immunity. These defects are further aggravated by chemotherapy making such patients susceptible to certain viral or fungal infections.

Cytotoxic chemotherapy has signigicant adverse effects on both B- and T- cell functions, resulting in diminished opsonizing activity, inadequate agglutination and lysis of bacteria, and deficient neutralization of bacterial toxins. Impaired antibody production has been described in untreated patients with chronic lymphocytic leukaemia and Hodgkin's disease (45).

The spleen serves as an efficient mechanical filter and as a source of opsonizing activity early in an infection. Splenectomized patients manifest diminshed antibody production when challenged with particulate antigens and have decreased levels of IgM and properdin. Hence, splenectonized patients are at increased risk of septicemia, usually with Streptococcus pneumonia, Neisseria meningitidis, or Haemophilus influenzae (46). Septicemia in these patients is characteristically fulminant and associated with large numbers of organisms in the blood stream. The incidence of postsplenectomy septicemia ranges from 1.4 to 20% in cancer patients and is especially dangerous in patients who are also receiving chemotherapy.

(46). Hence splenectomy is an imporant independent risk factor.

Severe malnutrition is common in these children and contributes to the loss of integrity of mucosal barriers, impairs phagocytosis, decreases macrophage mobilization, and depresses lymphocyte function (47). Hence the anorexia and cachexia associated with cancer necessitates aggressive nutritional support (elemental diets, supplements, parenteral alimentation).

The endogenous microbial flora exists as a carefully balanced synergistic microenviroment within the host. 86% of the infections which occur in cancer patients arise from the endogenous flora, although 47% of the infecting organisms are acquired by the patient during hospitalization (the most frequent isolates are Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia and candida albicans) (11). Numerous hospital sources may contribute to colonization of the patient, including staff to patient and patient to patient transmission (most frequently due to poor handwashing techniques) food, air, water, special equipment, medical and surgical procedures, especially intravenous therapy. Further-more, the endogenous microbial flora can be altered by antibiotics and chemotherapeutic agents. Hence when this occurs in conjunction with other host defects, infectious sequelae results.

Fever is common in cancer patients and may occur during 45-60% of hospital days. Only rarely can fever be attributed directly to the malignancy per se (e.g. the Pel-Ebstein fever of Hodgkin's disease). The majority (55 to 70%) of fevers occurring in these patients appear to have an infectious aetiology, especially when the patient is granulocytopenic (22,48). In this study 70.8% of fevers had an infectious aetiology and 28% were with severe granulocytopenia. The detection of infection and the initial management of the febrile-granulocytopenic patient is complicated by two factors: (a) The presence of granulocytopenia markedly alters the host's inflammatory response, making it difficult to detect the presence of infection. (b) An undetected and untreated infection can be rapidly fatal in

the granulocytopenic cancer patients. In this study there was neutropenia in 21 episodes of febrile illness. Eight occurred during Gram-positive infections and 4 during Gram-negative infections Four episodes of multiple infection were associated with neutropenia. Three cases of Varicella and one of measles occurred during severe neutropenia. Out of these 14 were fatal. Hence it is important to evaluate the febrile neutropenic patient carefully and then immediately initiate emperical broad spectrum antibiotic therapy.

Infectious agents Bacteria are responsible for most of the acute infections which occur in these patients. In this study 62.5% were aetiologically documented by bacterial isolates. Virtually any organism (even presumed non pathogens) can be the cause of an infection in the immunocompromised.

The Gram-negative bacilli (especially E. coli, K. pneumoniae, and Ps. aeruginosa) predominate in most institutions. Gram-positive bacteria (especially Staphylococcus aureus and the Streptococci) are also isolated frequently. In this study, the Gram-positive bacteria isolates superseeded the Gram-negative. Out of the 45 Gram-positive isolates 23 were due to Staphylococcus aureus and 12 due to Streptococcus. Of the 35 Gram-negative isolates 16 were due to Klebsiella, 9 due to E.coli and only 2 were Ps. aeruginosa which is the most frequent isolate in many studies. This study correlates well with that of Kaplowitz (25) who in his study of 113 admissions of children with leukaemia and lymphoma showed that Staphylococcus aureus was the most frequent isolates followed by E. coli and Klebsiella. Lopez and Fernandezperona (23) also showed in a study of 102 consecutive episodes of infection that 55% were Gram-positive bacteria and 45% Gram-negative bacteria. Staphylococcus aureus, Streptococcus pyogens and E. coli accounted for 55% of isolates. Other studies by James S. Miser and Angela W. Miser (28) and Stephen Ladisch and Philip A. Pizzo (24) showed that the organism most commonly causing blood culture positive infection in these children was Staphylococcus aureus. Chilcote and Boehner (21) showed that only 2 out of 37 isolates in their study was due to Ps. aeroginosa which is the most common organism isolated in other studies

Surprisingly, anaerobic organisms are an infrequent cause of infecti The relative distribution of the various organisms varies from institution to institution. Several centres have recently observed a decrease in Pseudomonas isolates while other Institutions have not an increase in the isolation of Gram-positive organisms (especially S. Aureus) (49).

Fungal infections (especially candida, Aspergillus, and mucormycosis) have been observed with increasing frequency (30). In this study most fungal infections were superficial 4 cases of Tinea corporis and one case of tinea capitis. Large patches of skin were involved but improved on topical antifungal agent. There was one case of systemic candidiasis which was severe and ended fatally.

The spectrum and severity of viral infections in these patients is wide and depends on age, prior exposure, immune response to the specific viral infection, as well as the underlying disease and the exposure to chemotherapy and radiotherapy. The human Herpes viruses (Herpes simplex I and II, varicella-Zoster, cytomegalovirus) are ubiquitious in nature and can cause both primary infection (herpes stomatitis, chicken-pox, mononucleosis syndromes) or can become latent and result in reactivation infections (gingivostomatitis, shingles) (34,35,36). In this study there were 4 cases of chicken-pox which were severe and ended fatally. 2 cases of measles, one was severe and the patient died in the acute stage. There was also 1 case each of Herpes labialis and Hepatitis.

Sites of infection The lung is the most frequent site of serious infection, followed by soft tissues (especially oro-rectal cellulitis) mucosal infection and septicaemia (51). Urinary tract infections are less common and central nervous system infections remain unusual. In this study it was seen that pneumonia occurred in 11 cases, stomatitis 11 cases, suppurative skin lesions and abscess 7 cases, anal ulcers 4 cases , pharyngitis 9 cases and septicaemia 17 cases.

Management

Septicemia: accountedfor 18% of the febrile episodes in this study Septicemia carries a high mortality and can not be reliably diagnosed by physical examination, rapid evaluation and the initiation of empiric antibiotic therapy is essential. This has been known to reduce the mortality and morbidity from septicemia in these patients.

The antibiotic therapy to patient with septicaemia depends on sensitivity of the microbial isolate. For patients with Gram-negative septicaemia, and aminoglycoside (e.g. gentamicin, tobramycin, amikacin) is generally combined with a semisynthetic penicillin (e.g. carbenicillin, tricarcillin). In this study we used gentamicin in combination with crystaline penicillin (as it is readily available The combination is necessary as an aminoglycoside alone is inadequate and penicillin alone results in development of microbial resistance. Most of the Gram-negative bacteria isolated in this study showed high sensitivity to gentamicin except Ps. aeurogrnosa which were sensitive to Amikacin. In cases of resistance to treatment parenteral or oral fixed combination formulation of trimethoprium - sulfamethoxazole (dose 20mg/kg/day of trimethoprium component) is employed successfully (30,31).

Treatment of Gram-positive septicaemia is successful with a cephalosporin or with a penicillinase - resistant penicillin (e.g. cloxacillin, methicillin) (24). In this study these drugs were not used but the patients started on gentamicin and crystalline penicillin and then the broad-spectrum discontinued after culture results to the appropriate antibiotic. In this study the Staphylococcus aureus and Staphylococcus albus were completely resistant to penicillin but showed high sensitivity to chlorampherical, minocycline and Co-trimoxazole.

These patients should be adequately treated for 10 to 14 days of antibiotics. If the septicaemia is associated with deep cellulitis or osteomyelitis they require 4 to 6 weeks of antimicrobial therapy.

In addition to antibiotic therapy, white blood cell transfusions ar beneficial in some patients with gram-negative septicaemias. This was not done in any of the patient in this study, though a few woul have benefited if the facilities were available.

Oral mucositis: Ulceration of the oral mucosa frequently occurs wi several commonly used chemotherapeutic agent (methotrexate, actino- mycin-D, adriamycin). In this study there were 11 cases of oral mucositis and this occurred when they were on methotrexate. 11 of them were bacterial isolates (Staphylococcus aureus 6, Streptococcu faecalis 2, Escherichia coli 1, Klebsiella 1) and Staphylococcus albus 1. This colonization may cause local infection or provide a portal for septicaemia.

Use of mouth- Cleansing salts and solutions (bicarbonate, hydrogen peroxide) may decrease or control the mucositis. Organisms like Candida ablicans are difficult to treat as oral Nystatin is of littl benefit; but patients do respond to short course of amphotericin B (0.5mg/kg/day for 7 days). One patient with candidiasis had a fatal outcome.

Otitis media: Common middle ear pathogens (S.pneumonia, S.pyogenes, H.influenzae) may cause otitis media, Gram negative organisms (Klebsiella, Psedomonas) must be considered. In this study there were 2 cases due to Staphylococcus aureus and one due to Klebsiella. Hence broad-spectrum antibiotic therapy must be instituted.

Eye: is rarely a primary site of infection in these patients; in this study there was one case of Staphylococcus aureus conjuncti- vitis.

Pulmonary infection: The lung is the most common site of serious infection in these children with haematologic malignancies. Cancer chemotherapy and radiation alter the host factors especially the alveolar macrophage. Mostly pneumonia occurs in association with neutropenia (and espicially septicaemia), and the mortality can be

as high as 80% (50). In this study there were 20 cases of pneumonia clinically and 11 of them were associated with septicaemia. 8 were due to Gram-negative organisms and 3 due to Gram-positive organisms. The isolates were 7 of Klebsiella, 1 of Pseudomonas, 2 of Staphylococcus aureus and 1 of Staphylococcus albus. During these episodes of pneumonia 12 were associated with neutropenia. There was one case of candida albicans involvement of the lungs.

The initial treatment include broad spectrum antibiotics, and if the patient fails to improve further evaluation is necessary to exclude other organisms (an open lung biopsy provides the highest diagnostic yeild). Other organisms which must be considered are Aspergillus, Candida, Cryptococcus, Histoplasma, Norcardia and Pneumocytstis carinii.

Gastrointestinal tract infections: The normal protective barrier of the gastrointestinal tract is altered by the underlying disease as well as by chemo- and radiotherapy induced mucosal defects. Since it is the reservior of micro-organisms, it serves as a portal for systemic infection in these patients.

Infection with common intestinal flora occurs but in addition there is a high risk of infection with anaerobic organisms, Salmonella and other Gram-negative bacteria especially Pseudomonas. In this study there were 3 episodes of Salmonella infection and 1 of Shigella. These patients are usually toxic and respond well to treatment.

Perianal infections are also common and usually occur after minor tears or ulcerations of the anorectal mucosa. They are usually due to gram-negative bacteria (51). In this study there were 4 episodes of perianal abscesses and the organisms isolated were staphylococcus aureus 2, Escherichia coli 3, and Streptococcus faecalis 1. The management in these cases is to put them on systemic antibiotic, keeping the wound clean, Sitz baths, warm peroxide compresses, low bulk diet and stool softeners.

Urinary tract infections: it is a relatively infrequent site of infection in children with haematologic malignancies. In this study there were 4 episodes, all of them due to gram-negative bacteria. There were 3 isolates of Klebsiella and 2 Escherichia coli. All responded well to treatment.

Cutaneous infections: The integrity of skin is frequently disrupted, especially byneedle punctures, biopies, surgery and radiation. Hence local cutaneous infections are common and may lead to disseminated infections. In this series there were 7 episodes most of them occurring after needle punctures. One occurred after abdominal surgery at the operation site and was due to Escherichia coli and Staphylococcus aureus. One child on admission had deep ulcers on the skin which occurredat the sites the traditional healer had made cuts. The organisms isolated from this case were Klebsiella and Citrobacter. Organisms isolated from infections due to needle punctures were mostly due to Staphylococcus aureus. In this study there were 7 such episodes. The management for these cutaneous infections is to keep the wound clean with antiseptic and systemic antibiotics.

Superficial fungal infections are also common and in this series there were 4 cases of Tinea corporis and one of Tinea capitis. There were large patches of skin involved and usually very itchy. They responded well to treatment with topical applications of an antifungal agent. Skin lesions may permit the early diagnosis of generalized infections, and fresh lesions should be aspirated (or biopsied) and the material cultured and examined with Gram-stain, KOH and acid-fast stain.

In cases of chicken-pox, vesicles appears on the body and the fluid can be cultured and examined under electron microscopy. The diagnosis is important as they need to be isolated. In this series there were 4 cases of chicken-pox and the outcome of 3 of them was fatal.

Musculoskeletal infection: Deep pyomyositis is rare but septic arthritis and osteomylitis do occur. They are usually due to Gram-negative organisms (Pseudomonas, Klebsiella, and Salmonella) or common Gram-positive organisms (Straphylococcus aureus).

Central nervous system infections: These are rare in children with haematolgoic malignancies (52). In this study there was one case of suspected meningitis but the C.S.F. was clear and no growth was obtained.

Control study done on patients without haematologic malignancies and who were not immunosuppressed showed a different spectrum of infections and the micro-organisms cultures were also very different from the study group.

CONCLUSIONS:

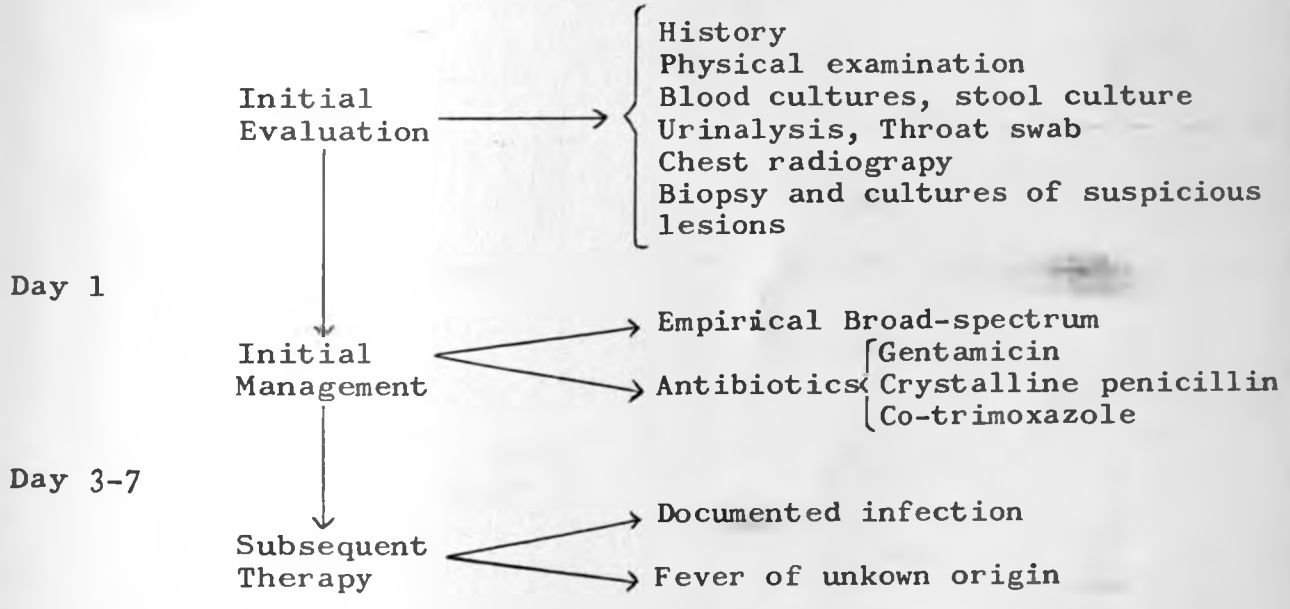
This study shows that in our institution (Kenyatta National Hospital) the micro-organism most commonly isolated from infective complications in children with haematologic malignancies was Staphylococcus aureus, followed by Klebsiella and Escherichia coli. Staphylococcus aureus was highly sensitive to Methicillin and Klebsiella and Eschrichia coli to Gentamicin.

Infections play a major role in morbidity and mortality in these children. This study showed 61.5% mortality due to infections.

RECOMMENDATIONS

This study shows that infections still remain a major complication in children with haematologic malignancies. Inorder to reduce the morbidity and mortality due to infective complications, it is of prime importance to recognize it, institute effective treatment and prevent serious infections.

Hence the febrile patient should be approached according to the following scheme:



The empirical broad-spectrum antibiotics should be initiated immediately after the evaluation and specimen collected. The drugs that are recommended are Gentamicin and Cloxacillin and should be given intravenously and Co-trimoxazole added if the child is neutropenic. It is however recommended to use carbanicillin (500mg/kg/day, i.v. every 4 hours) and cephalothin (17mg/kg/day, i.v. every 4 hours) to cover the Gram-positive infection (Straphylococcus and Streptococcus) and combine this with an aminoglycoside (Gentamicin or Amikacin) to cover the Gram-negative organisms. (Gentamicin - 6 mg/kg/day, i.v., every 6 hours).

From different studies it has been shown that even for specific Staphylococal infection broad-spectrum antibiotics should be used as Gram-negative infection occurs after specific use of antistaphylococal drugs.

It can not be over emphasized that recognition, evaluation and management of the infective complications in children with haematologic malignancies is the main stay in reducing the morbidity and mortality.

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APPENDIX I

INITIAL DETAILS FOR ALL PATIENTS INCLUDED IN THE STUDY

DATE ..... NAME ..... IP.NO .....AGE....SEX..

TRIBE .....

DIAGNOSIS ..... STAGE .....

STAGE OF TREATMENT

NEW PATIENT .....

INDUCTION .....

CYTOREDUCTION .....

INTRATHECAL .....

RADIOTHERAPY .....

MAINTANANCE .....

REMISSION .....

RELAPSE .....

RESULTS OF INVESTIGATIONS ON ADMISSION.

HEMOGRAM

WBC .....X10^9/L

RBC .....X10^{12}/L

Hb ..... g/dl

HCT .....

MCV .....

MCH .....

MCHC .....

POLY .....

STAB .....

LYMPH .....

MONO .....

EOS .....

BLAST .....

MYELOCYTES .....

METAMYELOCYTES .....

ANISOCYTOSIS .....

POIKILOCYTOSIS .....

PLATELET .....

RETIC .....

SED.RATE .....

BLOOD FILM .....

.....

.....

BONE MARROW RESULT .....

.....

CXR .....

SKELETAL SURVEY .....

IUP .....

LFT .....

U/E Na ..... K..... Ca.....UREA.....

URIC ACID .....

URINALYSIS .....

.....

STOOL .....

.....

APPENDIX II

PROFORMA FOR STUDY CARRIED OUT

CLINICAL FEATURES.

DATE .....

NAME ..... IP NO ..... AGE .....

DIAGNOSIS .....

C/O

DIARRHOEA .....JOINT PAIN .....

VOMITING .....BONE PAIN .....

COUGH .....EAR PAIN .....

O/E

PALLOR .....HGE TENDENCY.....EYES.....

TEMP .....JAUNDICE.....SKIN.....

MOUTH .....THROAT .....EARS.....

LYMPH NODES.....DYSUREA.....

COMMENTS .....

.....

ABDOMEN DISTRENSION .....LIVER.....cm MCL

SPLEEN .....cm MCL

OTHER MASS .....

COMMENTS .....

.....

CVS PULSE .....BP .....

HEART RATE .....

HEART SOUNDS .....

COMMENTS .....

.....

RESPIRATORY COUGH ..... PRODUCTIVE

PERCUSSION .....

ASCULTATION .....

COMMENTS .....

.....

.....

CNS ORIENTATION ..... CRANCIAL NERES .....

MOTOR SYSTEM ..... SENSORY SYSTEM .....

SIGNS OF MENINGITIS .....

COMMENTS .....

.....

.....

APPENDIX III

EPISODE OF INFECTION

DATE ..... NAME ..... IP.NO .....

TEMP ..... DURATION OF ILLNESS .....

C/S	ORGANISM	SENSITIVITY
BLOOD		
URINE		
STOOL		
SWAB		

OVA/CYST

URINE .....

.....

STOOL .....

.....

HEMOGRAM

WBC	.....$X10^9/l$	POLY	.....
RBC	.....$X10^{12}/L$	STAB	.....
Hb	.....g/dl	LYMPH	.....
HCT	.....	MONO	.....
MCV	.....	EOS	.....
MCH	.....	BLAST	.....
MCHC	.....	MYELOCYTES	.....
		METAMYELOCYTES	.....
		ANISOCYTOSIS	.....
		POIKILOCYTOSIS	.....
		PLATELET	.....
		RETIC	.....
		SED. RATE	.....

BLOOD FILM .....

.....

.....

VIRAL INFECTION .....

.....

.....

FUNGAL INFECTION .....

.....

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LIST OF TABLES