INFECTIVE ENDOCARDITIS IN CHILDREN ADMITTED TO KENYATTA NATIONAL HOSPITAL - A RETROSPECTIVE STUDY

A DISSERTATION SUBMITTED IN PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE (PAEDIATRICS), UNIVERSITY OF NAIROBI

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DECLARATION

This work is original and has not to my knowledge been submitted for a degree in any other University.

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CONTENTS

As Osler stated, "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire into what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations in the future."
Pediatrics 26: 993, 1960.

SUMMARY

This is a retrospective study, presenting the clinical and aetiologic features of infective endocarditis, in 45 children aged 0-15 years, seen over a six year period (January 1975 to December 1980), at the Kenyatta National Hospital.

The illness had been present for two weeks or less in 56% of the children. The majority presented with symptoms due to cardiac disease, and less commonly due to extracardiac problems. The most frequent clinical features were cardiac failure (88%), pyrexia (77%), splenomegaly (52%), renal manifestations (40%), and finger clubbing (33%); the other features occurred in less than 15% of cases. Anaemia (38%), leucocytosis (42%), and elevated ESR (52%) were also common.

Rheumatic heart disease was the underlying heart problem in 82%, congenital heart disease in 14%, combined rheumatic and congenital heart disease in 2%, and no pre-existing heart disease in 2%.

The blood cultures were positive in 31% of cases. The isolated organisms were species of either staphylococci, enterobacteriaceae, or a mixed culture.

It is concluded that infective endocarditis is common with a high mortality rate (42%). Organic heart disease is almost always present. The "classic" picture of the disease is rare. The positive blood culture rates are low. It is recommended that more laboratory diagnostic aid be utilised to support the diagnosis.

INTRODUCTION AND OBJECTIVES

Infective endocarditis(IE) or infection of the valves and endocardium was the term preferred by Thayer to emphasise the range of causative agents (1,2,3). The two previous entities of acute and subacute bacterial endocarditis do not reflect the nature of the causative organisms nor the course of the disease (4,5).

Aetiology falls under three categories: the predisposing factors, precipitating events, and causative organisms (3,5). The predisposing factors are underlying heart disease and compromised host resistance. The precipitating events serve as a portal of entry or as a source of the organisms. Portals of entry include any surgical manoeuvres such as catheterisations, intravenous lines, dental extractions, cardiac and abdominal operations. Any focus of infectioncan serve as a source of the organisms (1,6). Bacterial organisms form the majority of the agents where streptococcal and staphyloccal species account for over 90% of culture positive cases (7). Negative blood cultures do not exclude bacterial causes (8). Non-bacterial organisms that have been encountered include fungi, rickettisiae, chlamydiae, and viruses (7,8).

The clinical picture of IE is varied. The "classic" features are (7,10):

i) Persistent fever.
ii) Changing murmurs.
iii) Splenomegaly.
iv) Multiple positive blood cultures.
v) Peripheral embolisation such as Osler's nodes and Janeway's lesions.
vi) Vascular lesions such as petechiae, splinter haemorrhages, Roth's spots, and microscopic haematuria.
vii) Finger clubbing.

The last three listed features, excluding Roth's spots and microscopic haematuria can be grouped together as cutaneous manifestations. The pathogenesis of the clinical features is varied, and may be due to the local or to the distant effects of the pathologic process. The local effects are vegetations, perforations, tears, or myocarditis with consequent cardiac failure. The distant effects are due to emboli, metastatic infections, and immune complexes causing vasculitis or signs of hypersensitivity (2,9).

The antibiotic era caused a dramatic change of the "classic" picture such that presence of splenomegaly, finger clubbing, and changing murmurs were no longer part of the diagnostic criteria (7,10,11).

To promote earlier diagnosis, a "revised criteria" as proposed by Friedberg (11) consists of two associated findings of:

i) Unexplained fever of a duration of one week or longer, in the presence of
ii) An organic murmur or arterio-venous fistula.

In absence of either of these two, the diagnosis will depend on a positive blood culture or presence of embolic phenomena.

Recently, Gregoratos and Karliner (7) have proposed other "criteria for the atypical presentation" as the presence of any of the following:

a) Unexplained anaemia.
b) Stroke, or other neurologic manifestations.
c) Valvular heart disease with rapidly progressive symptoms.
d) Poorly controlled heart failure.

e) Glomerulonephritis, or any other unexplained renal manifestation.
f) Embolic occlusion of major peripheral arteries.
g) Multiple pulmonary emboli.
h) Saccular aneurysms, and
i) Post-operative cardiac patient who is not doing well.

The disease is still one of the few remaining infections with a high mortality rate the world over. This is mainly due to delay in diagnosis (1,12), which may be more so in the developing world. Very little work has been done on IE in Africa. The study that has been done in South Africa by Rose (13) was an autopsy review of IE in congenital heart disease. It revealed that 50% of clinically unsuspected IE was in children aged below three years. Somers et al (14) in Uganda looked at the pattern of IE at Mulago Hospital. Their patients were divided into those aged forty years and below, and those over forty years. Brenton et al (15) looked at the blood cultures in IE in all age groups at Mulago Hospital using meticulous techniques. Radia in Kenya (16) carried out a six-month prospective study on blood cultures in IE. The patients were aged between twelve and twenty years. These studies do not delineate the pattern or the causative organisms of IE in children. The clinical picture of this highly fatal illness with its associated aetiologic factors remain speculative in our children. This retrospective study was thus prompted with the aims of analysing:

1. The clinical features of IE as seen in children at KNH (Kenyatta National Hospital).
2. The associated underlying heart disease, and
3. The infective agents that were isolated.

MATERIALS AND METHODS

A. Selection of Cases:

a) Case files were reviewed for all children aged 0 - 15 years, who had a diagnosis of acute or subacute bacterial endocarditis, from 1st January, 1975 to 31st December, 1980, using International Classification Code Number 421.0.

b) Patients were included in the study if they met the requirements of the "revised criteria" (11) or "criteria for the atypical presentation" (7), as quoted in the introduction.

B. For each patient included in the study, the following was recorded:

a) Name, age, sex, and tribe.

b) Symptoms and their duration at the 1st or other presentation.

c) Clinical findings:
- Fever
- Cutaneous manifestations
- Cardiac findings
- Presence or absence of splenomegaly
- Neurologic and renal manifestations
- Foci of infection
- Prior surgical events

d) Laboratory data:
- Haemoglobin levels
- WBC count

- ESR
- Blood film
- Blood cultures and sensitivity pattern
- Other cultures
- Urinalysis
- BUN, ASOT, Khan, RA factor, Widal and Brucella agglutinations
- Echocardiographic findings
- Chest X-ray and ECG findings

e) Treatment for IE

f) Outcome

C. For patients with splenomegaly, tests done for other possible causes of splenic enlargement were recorded thus:

- Stool for Ova
- Rectal Snips
- Splenic aspirates
- Hb electrophoresis

RESULTS

Clinical Picture

There were 45 patients with IE over the six year period giving an annual admission rate of 7.5. The cardiac admissions for the same period were 511, giving an incidence of 8.8% of IE among cardiac admissions. Three of the patients had second episodes giving a total of 48 episodes, with a reinfection rate of 6.7%.

There was no difference in the sex distribution among the cases. The ages ranged from seven months to fifteen years. Two thirds of the children were ten years and over. The age and sex distribution is shown in Table I.

TABLE I

THE AGE AND SEX DISTRIBUTION IN THE 45 PATIENTS

AGE IN YEARS	NUMBER OF PATIENTS	
	FEMALE	MALE
>0 - 3	3	0
>3 - 6	2	2
>6 - 9	4	2
>9 - 12	7	8
>12 - 15	7	10
TOTAL	23	22

The tribal distribution for IE followed the tribal distribution of the cardiac admissions, as shown in Table 2. The "others" under IE represented one Ethiopian, one

TABLE 2

THE TRIBAL DISTRIBUTION FOR CARDIAC AND IE ADMISSIONS

TRIBE	% ADMISSIONS	
	IE	CARDIAC
Kikuyu	55.6	51.1
Kamba	8.9	11.0
Masai	6.6	2.2
Kalenjin	4.4	3.7
Luo	4.4	12.5
Tanzanian	4.4	0.4
Others	15.7	19.1
TOTAL	100.0	100.0

Zambian, and one each from the tribes of Embu, Kisii, Luyia, Meru, and Taita. The "others" under cardiac admissions represented twenty nine Meru, twenty eight Luyia, eighteen Kisii, five Somali, four Embu, two each from the tribes of Giriama and Digo, one each from the tribes of Taita and Turkana, one Asian, one Nubian, one Ethiopian, one Ugandan, and one Zambian. All the foreign children were Kenyan residents.

The symptoms at the time of presentation are shown in Table 3. These were either due to cardiac or to extracardiac manifestations of IE. The "others" in the table were single

- ESR
- Blood film
- Blood cultures and sensitivity pattern
- Other cultures
- Urinalysis
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TABLE 3

THE FREQUENCY OF THE SYMPTOMS IN THE 48 EPISODES

SYMPTOMS	EPISODES	
	NUMBER	%
Palpitations	29	60.4
Cough	26	54.2
Chest Pain	19	39.6
Dyspnoea	19	39.6
Abdominal Pain	15	31.3
Fever	14	29.2
Swollen legs	11	22.9
Vomiting	10	20.8
Joint pains	8	16.7
Haemoptysis	6	12.5
Weakness	5	10.4
Anorexia	3	6.3
Headache	3	6.3
Rigors	2	4.2
Others	5	10.4

episodes of oliguria, epistaxis, confusion, convulsions, and unconsciousness.

The duration of illness was within two weeks in twenty seven (56.3%), over two to eight weeks in eight (16.7%), and over eight weeks in six (12.5%) of the episodes. In seven episodes (14.5%), the duration of illness was not specified.

The frequency of the clinical signs is shown in Table 4.

TABLE 4

THE FREQUENCY OF THE CLINICAL SIGNS SEEN AT/DURING THE TIME OF ADMISSION IN THE 48 EPISODES

FEATURE	EPISODES	
	NUMBER	%
Cardiac failure	42	87.5
Pyrexia	37	77.1
Splenomegaly	25	52.1
Renal manifestations	19	39.6
Finger Clubbing	16	33.3
Neurologic manifestations	7	14.6
Haemorrhagic manifestations	7	14.6
Allergic rash	6	12.5
Central cyanosis	5	10.4
Others	2	4.2

Cardiac failure was intractable in seven episodes.

The temperatures ranged from 38.0°C to 40.5°C. The pyrexia followed no particular pattern.

Blood films in all the children were negative for malaria parasites.

The splenic size ranged from being just tipped to as large as 6 cm. Kala-azar and Schistosomiasis were excluded in the children resident in areas endemic for these diseases. Widal and brucella agglutination done in the toxic patients were negative. One three year old girl with a splenomegaly

of 4 cm had sickle cell anaemia. The spleen regressed on treatment for IE. A twelve year old girl, not included in the table, was from a highly endemic malarial area. She had a splenic size of 10 cm. Repeated blood slides for malaria parasites were negative. She was treated as a case of tropical splenomegaly syndrome, and the spleen did not regress with treatment of the IE.

In the nineteen episodes with renal manifestations:

a) eleven had microscopic haematuria .

b) three had elevated BUN.

c) three had both elevated BUN and microscopic haematuria. One of these children had red blood cell casts in the urine.

d) two had both elevated BUN and oliguria.

No other abnormality was noted on urine microscopy in any of these children. There was no proteinuria in any of the above cases and the blood pressures were within normal limits.

Finger clubbing occurred in 16 episodes, being associated with central cyanosis in 5 of these. Only one child who had both features also had severe congestive cardiac failure. None of these children had chronic liver disease, chronic suppurative chest infection, or cyanotic heart disease.

The neurologic signs in the seven episodes were:

(i) right hemiplegia - which was present on admission without any history of trauma. The skull x-ray was normal and the electroencephalogram did not demonstrate any focal signs.

(ii) right hemiplegia - which developed while on the ward. The first lumbar puncture yielded turbid CSF with normal sugar and protein and was negative for any organisms. A repeat lumbar puncture a few days later revealed uniformly blood stained CSF. This child expired.

(iii) Coma-thought to be secondary to midbrain emboli occurred in the same child who had left brachial artery embolus. CSF was normal except for polymorph leucocytosis with plenty of red blood cells on microscopy. This child expired on the same day.

(iv) Coma - in a child who lost consciousness for the first time and was brought to the hospital on the same day. Lumbar puncture yielded uniformly blood stained CSF without any organisms. She regained full consciousness two weeks after admission.

(v) right sided convulsions with right hemiplegia - these developed during her stay on the ward and she died on the same day.

(vi) a child who came in with a two day history of confusion. After some days' stay in the hospital, she developed a a stiff neck, aphasia, right hemiplegia, right facial and right hypoglossal nerve palsies. The CSF was turbid, but otherwise normal.

(vii) right eye blindness which was an incidental finding. Autopsy revealed emboli as the cause of right optic atrophy.

The blood pressures in these cases were within normal limits. None of these children had aortic stenosis or cyanotic heart disease as the underlying heart lesion.

The haemorrhagic manifestations included two episodes of epistaxis, splinter haemorrhages, petechiae, and one episode of bilateral subconjuctival haemorrhage.

An allergic rash appeared four weeks after commencement of antibiotic treatment in the 6 episodes. This maculo-popular rash was distributed over the trunk and extremities and was itchy in two of these cases. Penicillin and streptomycin were withdrawn and substituted by oral erythromycim. One of these children was treated with monthly benzathine penicillin and subsequent follow up revealed no evidence of penicillin allergy.

The "others" in the table represented two children; one had embolic occlusion of the left brachial artery, and the other had left popliteal artery aneurysm. Embolectomy and ligation of the artery were successfully done in these patients.

There were no surgical events prior to any of the episodes. Bronchopneumonia was present in 12 (25.0%) of the episodes. In three of these it was combined with diarrhoea in one child, scabies in another, and both a septic wound and a discharging ear in the third child. Urinary tract infection (UTI) due to proven E. Coli was present in one child. Throat swabs taken in 5 children with congested throat yielded normal flora.

The haemoglobin level was above 10g/dl in 25 (52.1%), ten or less in 18 (37.5%), and not available in 5 of the episodes. In those with haemoglobin levels of 10g/dl or less, the anaemia was normocytic and normochromic in 5, iron deficiency in 4, haemolytic in 4, dimorphic in 4, and not specified in one.

The white blood cell (WBC) count was 10,000/cmm or below in 20 (41.7%), above 10,000/cmm in 20 (41.7%), and not available in 8 of the episodes. The episodes with leucocytosis included

normal distribution in eight and neutrophilia in twelve.

The erythrocyte sedimentation rate (ESR) was elevated in 25 (52.1%), normal in 8 (16.7%), and not available in 19 of the episodes.

Underlying Heart Disease

The underlying heart disease is shown in Table 5.

TABLE 5

UNDERLYING HEART DISEASE IN THE 45 PATIENTS

HEART DISEASE	PATIENTS	
	NUMBER	%
Congenital		
Ventricular Septal defect	5	11.2
Patent ductus arteriosus	1	2.2
Rheumatic heart disease		
Mitral valve		
MI and MS	22	49.0
MI	2	4.4
Aortic valve		
AI and AS	2	4.4
AI	1	2.2
Mitral and Aortic valve		
MI, MS, and AI	6	13.4
MI, AS, and AI	2	4.4
MI and AI	2	4.4
Congenital and acquired Coarctation of the aorta and rheumatic AI	1	2.2
No underlying heart disease	1	2.2
TOTAL	45	100.0

Key MI = Mitral incompetence
MS = Mitral stenosis
AI = Aortic incompetence
AS = Aortic stenosis

Rheumatic heart disease (RHD), as the only acquired heart disease in this study, was the sole underlying organic heart problem in 37 (82.2%) of the patients. The children who had second episodes had RHD. The duration of RHD was available in 27 patients; it was within six months in 12, over six months to one year in 5, and over one year in 10. None of the children with RHD had the classical features of acute rheumatic fever. Anti-Streptolysin-O titre (ASOT)was available in 20 patients, and only significantly high in 13 of these children who had stigmata for IE. Two chidren with RHD had changing murmurs of MI and MS in one child and of AI and TI in the other child. Additional tests for other causes of fever associated with organic heart disease were done in few of the patients, at the discretion of the attendant doctors. These tests which were negative included RA factor, LE cell phenomena and Kahn test. The chest x-rays revealed cardiomegaly in all cases. Additional features variously reported in few of the patients were pulmonary oedema, pulmonary congestion, bronchopneumonia, pericardial effusion and pleural effusion. Echocardiograms were done in only two children and they revealed vegetations in one of them.

Among the five children with VSD only one had ASOT done, and it was negative.

The child with PDA had it successfully ligated. ASOT results in this child were not available.

The child with coarctation of the aorta had an elevated ASOT. Post-mortem supported the above diagnosis, and also revealed crumbly vegetations on the aortic valve, but even then pre-existing rheumatic valvular disease could not be ruled out.

The child without any previous underlying heart diseas was a seven year old Kikuyu boy from Kirinyaga. There was no history of any previous illness.

On admission, he was cachectic, very sick looking, had high fever with rigors, was in cardiac failure, and had no heart murmurs. He subsequently developed murmurs of TI and MI and a splenomegaly. He had microscopic haematuria, leucocytosis, elevated ESR, and anaemia. His chest x-ray revealed cardiomegaly with bronchopneumonia. Blood cultures yielded Citrobacter initially and Staph. albus subsequently. Other extensive investigations done for the cause of the fever were negative. Cardiac failure had improved until two days prior to his death when he suddenly deteriorated. The pneumonia had improved by the time of death. Autopsy was not done.

Causative Organisms

Blood cultures were done in all cases, as could be inferred from any of the following data in the files:

(i) the clinical follow up notes.

(ii) the laboratory reports.

(iii) the investigation sheets.

(iv) the discharge summaries.

The number of specimens withdrawn from individuals ranged from two to seven. The frequency of withdrawal was at the discretion of the attendant doctors as well as depending on the availability of the laboratory facilities. Attempts were made for first specimens to be taken off before commencement of antibiotic therapy in the majority of cases. Out of the 48 episodes 15(31.3%) were positive, 29(60.4%) were negative, and results were not available in 4(8.3%).

The breakdown of the positive blood cultures is shown in Table 6. Multiple positive blood cultures were seen in

TABLE 6

THE POSITIVE BLOOD CULTURES RESULTS IN THE 15 EPISODES

ORGANISM	NUMBER OF EPISODES
Gram positive	
Staph. albus	4
Staph. aureus	3
Gram negative	
Klebsiella	2
S. typhimurium	1
E. coli	1
Mixed cultures	
E. coli and Staph. aureus	1
E. coli and Strep.faecalis	1
Klebsiella and S.typhi	1
Citrobacter and Staph. albus	1
TOTAL	15

staphylococcal IE. Staph. albus was isolated in three specimens in one child, in two specimens in two children, and in one specimen in one child; Staph. aureus was isolated in three specimens in one child, in two specimens in another child, and in one specimen in the third child. E.coli and Strep.faecalis were grown from one bottle. The remaining mixed cultures were grown from different specimens taken at

different times. The majority of the positive culture specimens were in the first of the samples taken. The clinical picture could not be related to the causative organisms.

Among the culture negative cases was a fourteen year old Masai boy who was treated as a case of Chlamydial IE. Serology in this child was positive. No other tests for non-bacterial IE were done in any of these children. Echocardiograms were done in two of these patients.

Outcome

Of the 45 patients, 17 (37.8%) are lost to follow up, 4 (8.9%) were sent back to be followed up by the referring hospitals, 5(11.1%) are still being followed up at KNH, and 19 died (two of them during the second episode) giving a mortality rate of 42.2%. Death was due to cardiac failure (7), cerebral embolism (2), and the cause of death in single patients included:

i) midbrain embolism with subarachnoid haemorrhage.

ii) pulmonary embolism.

iii) Cerebral infarcts and pneumonia.

iv) Cardiac arrest a few hours following mitral valve replacement, and

v) during cardiac catheterisation.

The causes of death were not available in the remaining 5 children.

The various features in the 19 deaths are shown in Appendix A. The comparison of the rates at which these features occurred among the deceased and the 26 survivors is shown in Table 7. There was no statistically significant difference among the two groups of patients.

TABLE 7

THE FREQUENCY OF THE VARIOUS FEATURES AMONG THE SURVIVORS AND THE DECEASED

FEATURE	FREQUENCY	
	% SURVIVORS	% DECEASED
Age $\geq$ 12 years	50	63
$\leq$ 11 years	50	37
Sex - Females	62	37
- Males	38	63
Sick looking	54	53
Cardiac failure	88	100
Pyrexia	81	84
Splenomegaly	50	63
Microscopic haematuria	30	32
Elevated BUN	12	26
Finger Clubbing	46	21
Neurologic problems	12	21
Bronchopneumonia	23	32
Leucocytosis	38	53
Anaemia	42	37
Mitral valve disease	65	68
Culture positivity	38	26
Culture negativity	58	53

Key Mean age = 11 years

DISCUSSION

Clinical Features

The annual admission rate of IE (7.5) in this study was high compared with that of 1.8 to 3.0 in the western countries (2,17,18). This discrepancy may be due to the less rigid criteria for diagnosis of this condition. In contrast, the rigid criteria used in some studies in the western countries (6,17,19) would by current view miss out 90% of the patients (7,10). The observation by Steiner et al that IE may be commoner in Africa compared with the western world (20), could be a reflection of the more effective prophylaxis against rheumatic heart disease (RHD) in those countries (4). The high incidence of IE among cardiac admissions may be due to the fact that not all cardiac patients are admitted to the wards, many being treated in the paediatric observation ward.

The equal sex distribution has been noted by other workers (18,19). The increasing frequency of IE with rising age in the present study may be due to the higher rate of RHD after the age of three years; the risk of developing IE in congenital heart disease (CHD) increases from 6.6% to 16.5% in children above two years of age (1,18).

The highest rate of the Kikuyus is a reflection of the predominant tribe in the area served by this hospital. KNH is also the national referral hospital.

The symptoms due to cardiac disease were the commonest. The features of constitutional upset as may be seen in any infection included fever, vomiting, joint paints, weakness, anorexia, headache, and rigors. These features were seen in only a few patients. They could not be related to the invasive properties of the organisms, contrary to the observation made by Weinstein and Schlesinger (9). Other symptoms like oligaria, convulsions and coma demonstrate

the trend towards the atypical presentation, as noted by Weinstein and Rubin (10).

The majority of the patients sought medical advice within the first eight weeks of illness, as noted by other workers (14,18,21). The history may sometimes be unreliable as an index of how advanced the disease is. This is because some parents will give a shorter history so as not to appear negligent. The very insidious nature of the illness may be an additional contributory factor (22). RA factor could not be used as a guide to the duration of illness since it was done in only a few episodes 4/48. RA factor is positive in 50% of cases who have had the disease for longer than six weeks (10).

Cardiac failure (87.5%) was the commonest finding, as has been observed elsewhere (7,14). The lesions causing failure have been enumerated (9,10) and these include:

a) Involvement of the valves with consequent -
   i) erosion of the edges of the valves
   ii) weakening of the valvular substance leading to prolapse and/or perforation
   iii) total destruction by highly invasive organisms
   iv) valvular stenosis.

b) Rupture of chordae tendinae.

c) Myocarditis - the actual mechanism is still controversial but postulates include:
   i) Ischaemia secondary to coronary emboli
   ii) Toxins produced by the organisms
   iii) direct invasion by the organisms
   iv) deposition of immune complexes.

d) Extension of infection through myocardial wall with resultant fistulae, aneurysms, perforations, septal defects, cardiac tamponade, and myocardial abscesses.

e) Rupture of infected sinus of Valsalva.

The responsible lesions could not be verified in this study since post-mortem which was done in only 3/19 of the deaths did not report any special findings, and no operation was done for any child with intractable cardiac failure.

Pyrexia (77.1%) was common, as has been reported elsewhere (1,7). It may be absent in certain cases such as: a) massive intracerebral or subarachnoid haemorrhage b) severe congestive cardiac failure c) uraemia d) advanced age and e) prior antibiotic therapy (7,10). None of the apyrexial children fell in any of these categories, excluding the latter cause which would be very difficult to rule out.

Splenomegaly (52.1%) compares well with the reported rates of 50 to 66% (4,6,14,18). The enlargement which is due to lymphatic hyperplasia and enlarged malpighian bodies is a reflection of the RES response to unrelenting infections like IE (1). Blumethal et al related presence of splenomegaly to advanced disease (2). This was not possible in this study because the narrated duration of illness may be unreliable. However, since two thirds of the children who were sick-looking on admission had or developed Splenomegaly later on, this may be in agreement with the observation made by Blumethal et al, more so since there was a high mortality (44.0%) in these patients.

Three types of renal lesions have been described: focal embolic glomerulitis, acute glomerulonephritis (AGN), and chronic glomerulonephritis (7,10). The children

who had microscopic haematuria with or without elevated BUN were possibly having immune complex vasculitis, those with oliguria and elevated BUN were manifesting AGN, whereas those with elevated BUN only had embolic infarcts. The AGN is immune complex rather than embolic in origin (7). The rate of microscopic haematuria (29.2%) compares well with that of 30.0% found in Mulago Hospital (14).

Finger clubbing (33.3%) in this study was within the rates of 12 to 52%, as found by other workers (7,10,14,18). Cyanosis (11.1%) and finger clubbing in our patients may have been due to the severe congestive cardiac failure, although only one child with both features died from uncontrollable cardiac failure.

The neurologic complications (14.6%) compares well with that of 16 to 25% (6,14). The reason for the predomiant right sided manifestations is probably anatomical. The turbid CSF raises IE as a differential of meningitis.

The haemorrhagic problems (14.6 %) have ranged from 4 to 30% (14). These are due to immune complex vasculitis causing increased capillary permeability (1).

The allergic rash (12.5%) was confused for penicillin allergy, a factor that would interfere with chemotherapy, as was the case in this study. It cannot be over emphasised that a history of penicillin allergy be ruled out right from the start. This rash is a hypersensitivity manifestation due to circulating immune complexes (23).

Left brachial artery embolus was present in one child whose blood culture grew Staph. aureus. Large vessel emboli result either from non-bacterial organisms (8), or

from the more invasive bacteria like Staph. aureus, pneumococci, and H. influenzae (9). The child with left popliteal aneurysm had no organisms isolated from his blood. Mycotic aneurysms may result either from direct bacterial invasion of the arterial wall or from embolic occlusion of the vasa vasorum (7). The latter was possibly the mechanism in our child.

The absence of Osler's nodes and Janeway's lesions in this study is note worthy. These features are rare in children (1,22), and besides if not looked for can be easily missed.

Surgical manipulations are not invariable before IE (17). The postulated portals of entry in this work include raw areas after shedding of teeth, dental extractions, skin abrasions, therapeutic marks, and wounds left by intravenous therapy. The foci of infection (27.1%) was within the observed range of 25 to 62% (14,18,19). This rate may have been higher if the foci had been looked for in our patients. Dental and skin sepsis are common in our community (24). Chewing has also been incriminated in causing bacteremia (25).

The rate of anaemia (37.5%) may well compare with the reported rates of 50 to 80% (7,10). This is because of the lower haemoglobin level at which anaemia is defined in our set up (26,27).

Leucocytosis (41.7%) was comparable to the reported rate of 50% (18). It may be due to neutrophilia or be associated with normal distribution (2,10), both of which were encountered in our patients.

ESR was elevated in 52.1% in the present study. Rates of 60 to 90% have been reported by other workers (10,18).

Underlying Heart Disease

RHD accounted for 82.2% and CHD for 14.0% of the underlying heart disease; this contrasted with the cardiac admissions where both were equally represented. This is because although acute rheumatic fever is common in Kenya (24), the majority of our patients are treated in dispensaries where prophylaxis is usually not given. Thus many children with RHD go unrecognised in our community, until they develop a complication like cardiac failure or IE. This is further supported by the relatively short history regarding RHD. In contrast, the children with CHD are usually referred to KNH resulting in their high admission rates. CHD is, however, the underlying heart disease in 66 to 75% of IE in the western world where RHD accounts for only 33% (2,5,18). The low contribution of RHD in those countries is attributed to both the prophylactic prevention of RHD (4) and the improved standards of living reducing the incidence of acute rheumatic fever (5).

All the valvular lesions were clinical diagnoses. A study comparing the clinical and autopsy diagnoses revealed, that the location of the lesion was almost always accurate. In contrast, further diagnosis of incompetence or stenosis was frequently incorrect (19). Thus a discussion of the affected valve is more meaningful than the actual lesion. The predominance of mitral valvular disease in this study is in agreement with the commonest valve affected by RHD in Kenya (24). A similar involvement has been noted in North America (7).

VSD formed the majority of the CHD in this study as compared to elsewhere where tetralogy of Fallot was the commonest, followed by VSD (1,13,17). None of these children, nor the child with PDA had pulmonary embolism, as would be

expected in right heart IE. The incidence (2.3%) of IE among our patients with CHD is low, this is especially so considering that 5 of the 6 children with CHD were above two years of age. The reported risk of IE above this age is 16.5% (1,18). We may be missing these cases, as observed by Rose (13).

Combined CHD and RHD was reported in a child who had coarctation of the aorta with mitral incompetence (18); our patient had aortic incompetnece.

There was only one child without any pre-existing heart disease, compared with the high frequency of 9 to 40% (7,14,19). This type of IE is part of a generalised sepsis with a focus of infection. It is usually found in children under two years of age in those with compromised host resistance (1). This was a seven year old who had bronchopneumonia and in whom blood culture yielded a mixed growth of Citrobacter and Staph. albus. There was no evidence of compromised host resistance and no supporting evidence for drug addiction. The latter has not been described in this hospital's admissions of this age group.

Echocardiography (Echo) came into use at KNH after July 1979, thus the apparent under utilisation. Its diagnostic value has long been recognised (28). Although only vegetations bigger than 3mm can be picked up, repeat echocardiograms may prove positive (28). The major contribution of this test is in patients with negative blood cultures since non-bacterial agents tend to cause large vegetations (8); the majority of the patients in this study were culture negative. This test demonstrated presence of vegetations in one of the two culture negative children in whom it was done. Echo, however, does not differentiate between active and healed lesions (7).

The chest x-ray and ECG findings were those of underlying heart disease, as has been reported (7). In addition, chest x-rays ruled out chronic chest pathology that may be associated with features of IE such as finger clubbing and central cyanosis.

Causative Agents

The rate of positive blood cultures (31.3%) was low compared with that of 76 to over 80% found by Somers et al working in Kampala (14) and by Cutler et al working in North America(18). IE in our set up may be more commonly due to culture negative causes. This is supported by unpublished work done at KNH on blood cultures in IE using meticulous techniques. No organisms were isolated in the 12 patients seen (16), as compared to the yield in 4/15 patients seen at Mulago Hospital (15).

The isolated organisms were classified into Staphylococci and Enterobacteriaceae. The isolation of multiple organisms in this study is unexplained since there was no faecal contamination of any of the blood culture specimens. Mixed infections of a streptococci with any other organism were reported in 5.4% of cases in a reviewiby Lerner and Weinstein in North America (3).

Skin abrasions, therapeutic marks, and intravenous therapy were thought to be major portals of entry for the Staphylococci. Enterobacteriaceae are forced to enter the blood stream during abdominal operations or by instrumentation such as sigmoidoscopy, which stretch the mucosae (4). None of the children with these organisms had those manipulations. One may postulate that abrasions in the perianal region, as may occur with diarrhoea may act as a portal of entry for these organisms.

Intestinal parasites are common in Kenya (24). Infestations of the large colon with amoebae and Enterobius vermicularis

cause breaks in the colonic mucosa and may thus permit entry of normal flora into the blood circulation.

The negative blood culture rate (60.4%) was high compared with rates of 2 to 25% (7,8,14). The causes of negative cultures may be bacterial or non-bacterial (7,8). The non-bacterial causes have been enumerated in the introduction. The bacterial causes include:

i) Poor bacteriologic techniques and organisms needing special growth requirements and these are:

   a) Anaerobic bacteria
   b) Satelliting Streptococci
   c) Streptococcal mutants-thiol-requiring
   d) L-forms
   e) Brucella.

ii) Prior administration of antibiotics before blood culture samples are drawn.

iii) Right sided IE

iv) Uraemia

v) Very chronic (bacteria-free stage) IE

vi) Mural IE

Poor specimen collection techniques must be stressed in our set up. Too often in this hospital only one type of culture medium is available and sometimes none at all. Ideally, three culture media should be used for a single set of cultures. There is no protocal regarding taking of blood culture samples in IE at KNH. It was not unusual

in this study to find repeat blood samples that were taken two to three weeks after commencement of antibiotic therapy in a previously culture negative patient. The amount of blood drawn off may be too little compared with the recommended amounts (8). These drawbacks make it difficult to gauge the true rate of culture yields in our cases. The contribution of bacteria that are difficult to culture, such as Brucella and Satelliting Streptococci in our community is thus not known. One case of satelliting Streptococci was reported in Kampala among the four unusual bacterial organisms that were recovered (15). Whereas L-forms should be considered in patients who had received antibiotics, they have also been cultured in patients in absence of prior therapy (8).

The role of prior antibiotic therapy is controversial. One study showed that prior treatment had no effect on culture positivity (29); another study showed that positivity for streptococcal species IE was reduced by 6% (30). The relevance of these findings to our children is not known.

Right sided IE was not associated with negative blood cultures in this study. Three of the five children with VSD had positive blood cultures yielding Staph. albus in two, and Staph. aureus in one. The blood culture of the child with PDA yielded E.coli and Strep. faecalis from the same bottle.

The two children with elevated BUN and oliguria were both culture negative. The mechanism of culture negativity in uraemia is not known (8).

Negative cultures in this study could not be related to duration of illness. Autopsy may define the role of bacteria-free stage when cultures from vegetations yield organisms in

patients that have been negative clinically, as was seen in some cases in Kampala(21).

Echo and more frequent autopsy may delineate the role of mural IE in our patients. VSD may be associated with isolated mural IE (8).

Finally, although bacteremia associated with IE is qualitatively continuous, it is quantitatively discontinuous (8). This latter quality may be responsible for a few cases of negative cultures in the children studied.

One child in this study had Chlamydial IE. Another child has just been proved Candida albicans IE, as this work goes to print. We may be missing rickettisial IE. Only one case of viral IE has been described so far in a case of mural IE in which cytomegalo virus and bacteria were isolated (31).

It is surprising that no Strep. viridans was isolated. This organism, which has been the cause of IE elsewhere in 50 to 87% of cases (2,3,18.19), may not be a common cause of this disease in our environment. A review comparing IE in the pre-antibiotic and the antibiotic era in North America (10) revealed interesting microbiologic changes which included:

a) A fall in streptococcal IE from 90% to 35%, with a decrease in incidence of Strep. viridans and appearance of other Streptococcal species. This may partly explain the paucity of Strep. viridans IE at KNH.

b) A rise in staphylococcal IE from occassional to 20% of cases, where Staph albus IE was unknown prior to advent of antibiotics. Staph. albus IE is frequently observed following open heart surgery (3,7); although none of our children had any prior surgery.

c) Uncommon bacteria such as Enterobacteriaceae which were rare are the cause in 5 to 10% of cases today.

d) Only 2 cases of fungal IE were reported prior to the antibiotic era. Today the infection is occasionally seen in special circumstances such as post-operative cardiac patient, narcotic addicts, and in systemic fungal infections (3,7). These circumstances will assume greater importance with time as technology advances, and situations leading to compromised host resistance increase such as cytotoxic therapy, drug addition, and broad spectrum antibiotic treatment.

e) The incidence of rickettsial IE is still unknown, and that of viral IE is still very rare.

The trend towards Staphylococcal and Enterobacteriaceae IE is well demonstrated in this study. A similar trend was seen in Mulago Hospital where Staphylococcal and Streptococcal IE was of equal frequency and Enterobacteriaceae were seen in 5/33 of their culture positive cases (14).

Outcome

The mortality (42.2%) in the present study was high compared with that of 17% (2,18). The possible reasons for this high mortality were: presentation of patients at advanced stage of illness, difficulty of arriving at the diagnosis, and non-aggressiveness in surgical therapy.

Several diseases mimic IE, more so in a tropical environment. Many of these patients were treated at the local dispensaries where patient over-load leads to blind treatment for the local disease priorities. This fact together with the insidious and non-specific nature of the illness may have

contributed to the late presentation of these children to KNH, with consequent delay in starting specific antibiotic therapy. Prognosis is better in earlier initiation of treatment (22). At the national hospital, poor specimen collection techniques that have been recounted above may have played a major role in causing delay at reaching the diagnosis. Only isolation of the causative agent from the blood can confirm the diagnosis, and prognosis is better in culture positive IE (22). Indications for surgical management include (7,22): intractable or rapidly progressive cardiac failure, persistent infection, prosthetic valve IE, and certain extra-cardiac complications such as aneurysms and major vessel emboli as was seen in this work. Defective chemotherapy (22,32) contributed towards 4 deaths in our patients. The underdosages were crystapen alone ½ mega units six hourly in a fourteen year old, crystapen alone 4 mega units eight hourly in a fourteen year old, capsule ampicillin 500 mg six hourly in a twelve year old, and crystapen ½ mega units six hourly in combination with adequate doses of gentamycin in a nine year old.

Cardiac failure was the single most common cause of death, as noted by other workers (9,10,11,19). Cerebral embolism was associated with a high mortality, as found by Somers et al in Uganda (14). Pulmonary embolism has been reported to be of no prognostic value in a study where it occurred in 10% of cases (19), although it was responsible for 2 deaths in this study. In the 5 children in whom the cause of death was not specified, it is speculated that cerebral midbrain or pulmonary embolism may have caused sudden death; septicaemia, uraemia, or cardiac failure could not have been missed.

Although, statistically, none of the features was found to be of any prognostic value, certain of these features deserve special mention.

IE associated with a focus of infection such as bronchopneumonia tends to be due to virulent organisms and is, therefore, associated with a high mortality. Half of the children who had bronchopneumonia in this study expired.

Mortality in those patients with renal manifestations was high. Uraemia was the cause of death in 6/50 fatalities (11), and in 8/442 patients (19).

Staphylococcal IE is associated with a lower recovery rate (22); the gram negative bacteria are difficult to cure (32). These were the types of organisms encountered in this study and may partly explain the high mortality rate.

Fatality is higher in culture negative individuals (10). Factors which prohibit organisms from being shed into the blood stream may prevent antibiotics from getting to the organisms (1). Effective therapy is difficult to apply in the absence of specific diagnosis (10).

Factors operative among the patients lost to follow up may be socio-economic problems, population mobility, or death. Embolisation which may lead to sudden death is known to occur even in patients whose infection has been controlled (2).

The re-infection rate of 6.7% in this study is comparable to that of 8.2% (1).

CONCLUSIONS

1. IE is relatively common in our set up.

2. The presenting symptoms are those of cardiac disease, followed by those of constitutional upset, and those due to the distant effects of the disease, when the patients may initially present to various specialists.

3. Fever and features of cardiac failure are frequent. Splenomegaly, renal manifestations and finger clubbing are common. Neurologic and haemorrhagic features, central cyanosis and allergic rash are less common. Other features are occassional. Foci of infection are common. The "classic" picture is unusual; only one child nearly portrayed this picture.

4. Organic heart disease is almost always present. The majority of cases have RHD, CHD is less common, while a combination of both is rare. IE on a previously normal heart is rare.

5. Anaemia, leucocytosis, and elevation of ESR are common.

6. Chest x-ray and ECG are of no diagnostic value, but are useful as baseline, and for detection of complications. The role of echocardiography remains to be seen.

7. The positive blood culture rates are low. The isolated agents were species of Staphylococci, Enterobacteriaceae, or a mixed culture of both.

8. The mortality rate is high. The major causes of death are cardiac failure, neurologic complications, pulmonary embolism and defective therapy. None of the other features was of any prognostic value.

RECOMMENDATIONS

1. IE is a very difficult diagnosis to make, especially in absence of positive cultures. More laboratory diagnostic aid may help to support the diagnosis.

   (i) Echocardiography should be done in culture negative patients (8).

   (ii) Ear lobe peripheral films for histiocytes and macrophages, as evidence of the stimulated RES (1).

   (iii) Circulating immune complexes by the polyethylene glycol (PEG) precipitation test is positive in 84% (22).

   (iv) Bone marrow aspirate can be cultured particularly in patients who have been on antibiotics (2,21).

2. An attempt should be made to increase the rate of culture positivity. To increase the yield (21), it is recommended that :-

   a) At least three to six sets of blood specimens should be drawn over a period of 48 hours.

   b) The ratio of the blood to the liquid culture medium should be 1:10 to 1:20.

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   b) The ratio of the blood to the liquid culture medium should be 1:10 to 1:20.

3. The organisms isolated suggest there may be need to change the first line of drugs, using gentamycin instead of streptomycin to cover Staph. albus.

4. IE just like meningitis, should be given labels such as Staph. aureus IE or culture negative IE. These labels give important connotations regarding both therapy and prognosis (2).

5. The thoracic surgeons should be consulted in cases with intractable cardiac failure.

THE VARIOUS FEATURES IN THE 19 DEATHS

SERIAL NUMBER	AGE IN YEARS	SEX	SICK LOOKING	CCF	PYREXIA	SPLENOMEGALY	HAEMATURIA	↑BUN	FINGER CLUBBING	NEURO	HAEMORRHAGIC	BRONCHOPNEUM	LEUCOCYTOSIS	ANAEMIA	HEART DISEASE	BLOOD CULTURE	CAUSES OF DEATH
1	13	F	–	+	+	–	–	–	–	–	–	–	N/A	–	MI & MS	Staph. aureus	CCF
2	15	M	–	+	+	+	+	–	–	+	+	–	–	–	MI, MS & AI	–	Cerebral infarcts & pn
3	10	M	+	+	+	+	–	–	–	–	–	–	–	+	CO-AO & AI	–	CCF
4	11	F	+	+	+	–	–	+	–	–	–	+	+	+	MI	–	Cardiac arrest
5	14	M	–	+	+	–	–	–	–	–	–	–	+	+	MI, MS & AI	S. typhim	CCF
6	15	M	+	+	–	+	–	–	–	–	+	+	+	–	MI & MS	–	CCF
7	15	M	+	+	+	+	+	+	+	+	+	–	+	–	MI, MS & AI	Staph. aureus	Midbrain emboli and S-Arach
8	9	M	+	+	+	+	–	–	–	–	–	+	N/A	N/A	MI & MS	N/A	N/A
9	14	M	+	+	–	–	–	–	+	–	–	+	+	–	MI & MS	–	CCF
10	12	M	+	+	+	+	+	–	–	–	–	–	–	–	MI & AI	–	During Cath.
11	12	F	–	+	+	–	+	+	–	–	–	–	+	–	VSD	–	N/A
12	14	M	+	+	+	–	–	–	–	+	+	–	+	–	MI & MS	N/A	Cerebral embolism
13	7 mo.	F	–	+	+	+	–	+	–	–	–	+	+	–	VSD	Staph. albus	CCF
14	7	M	+	+	+	+	+	–	–	–	–	+	+	+	NONE	Citrob & Staph albus	N/A
15	15	F	–	+	+	–	–	–	+	–	–	–	+	+	MI & MS	–	Pulm embolism
16	10	F	–	+	–	+	–	–	–	–	–	–	+	+	MI, AI & AS	–	Cerebral embolism
17	14	M	+	+	+	+	+	–	+	–	–	–	N/A	N/A	MI	N/A	N/A
18	13	F	–	+	+	+	–	+	–	+	–	–	–	+	MI & MS	–	CCF
19	8	F	–	+	+	+	–	–	–	–	–	–	–	–	MI & MS	–	N/A

Key – on next page.

CCF = Congestive Cardiac failure

M-h'turia = Microscopic haematuria

↑-BUN = Elevated blood urea nitrogen

F-Clubbing = Finger clubbing

Neuro = Neurologic manifestations

H'morrhagic = Haemorrhagic

Br-pneum = Bronchopneumonia

Leuco = Leucocytosis

+ = Positive - = Negative

N/A = Not available

MI = Mitral incompetence

MS = Mitral stenosis

AI = Aortic incompetence

AS = Aortic stenosis

CO-AO = Coarctation of aorta

VSD = Ventricular septal defect

S.typhim = Salmonella typhimurium

Citrob = Citrobacter

pn = Pneumonia

S-Arach = Subarachnoid haemorrhage

Cath. = Cardiac catheterisation

Pulm = Pulmonary

ACKNOWLEDGEMENTS

My appreciation and thanks are extended to the following who contributed towards the achievement of this work:

1. My two supervisors, Dr. S.K. Shah, and Dr. M. Lumba for their continued guidance and criticisms.

2. Dr. H.O. Aseso and Dr. J.O. Ndinya-Achola who initiated my interest in this topic, for their support and encouragement throughout the production of this work.

3. The staff of the Medical Records Department, Kenyatta National Hospital, for their tireless work in the provision of the patients' files.

4. Mr. W. Gemert - Biometrician at the Medical Research Centre, Department of Royal Tropical Institute of Amsterdam, Kenyatta National Hospital, for the statistical analysis.

5. The WUS (World University Services) whose sponsorship made it possible for me to undertake this course.

6. Miss Ruth Kanya for the excellent secretarial work.

7. My son Adam and my sister Anne for their patience and understanding during the pursuit of this work.

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