Antibiotic use in infants hospitalised with HIV-related pneumonia in Harare, Zimbabwe

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Abstract

Objective : To describe the clinical features of infants admitted with HIV-related pneumonia and to describe antibiotic use in relation to recommended treatment guidelines.
Design: Case series.
Setting: Paediatric medical wards of two University Teaching Hospitals, Parirenyatwa and Harare Central Hospitals.
Subjects: 100 infants aged one to12 months admitted with HIV-related pneumonia
Main Outcome Measures: Mortality and antibiotic use in the two hospitals.
Methods: Records of 100 infants admitted for 48 hours or more with features of HIV-related pneumonia were analysed for clinical features and antibiotic use.
Results: 77% of patients were in the first six months of life with a peak age of two months and a median of four months (Q_1 = 2, Q_3 = 6). The median age of children admitted to Parirenyatwa hospital was 5.5 months (Q1 = 3, Q_3 =7) and in Harare hospital it was three months (Q_1 = 2, Q_3 = 6). The difference was statistically significant, p=0.035.
Fifty four percent of cases received penicillin, aminoglycoside and cotrimoxazole and overall only 30% of prescriptions complied with Essential Drug List of Zimbabwe (EDLIZ) recommendations for treatment of severe pneumonia in children with HIV infection.

The overall mortality was 27.0%. The mortality in Harare Central Hospital was 40.4% and 15.7% in Parirenyatwa. The difference was statistically significant p= 0.005.
Conclusion: The difficulties in establishing the cause of the pneumonia in infants with HIV infection was a contributory factor to lack of adherence to standard treatment guidelines. In countries with a high prevalence of HIV infection and with limited resources, a clinical case definition for *Pneumocystis carinii* pneumonia (PCP) is required as a measure to provide treatment for infants with HIV related pneumonia which is evidence based. This approach will also promote rational antibiotic prescribing and will contain cost.

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Introduction

AIDS is now the biggest single cause of child death in Zimbabwe reversing years of steady progress in child survival.[1] In Harare the infant mortality rate doubled from 30 to 60 per 1 000 between 1990 and 1996 and in the under five year olds the mortality rate almost trebled from eight to 20 per 1 000 in the same period.[2] Such high infection rates will have far reaching effects on the health sector putting additional strain on an already overburdened health care system in the country.

HIV Diagnosis in Children.

The diagnosis of HIV/AIDS infection in children is based on clinical signs and laboratory investigations. Clinical signs commonly found useful for diagnosis of HIV infection are recurrent infections; oral thrush; persistent fever; persistent diarrhoea; generalised lymphadenopathy; developmental delay; weight loss or failure to thrive; severe or repeated pneumonia;severe pruritic dermatitis; chronic parotitis; persistent hepatosplenomegaly; opportunistic infections; neoplasms and neurological involvement.[3]

The laboratory diagnosis of HIV infection in children is made by either antibody testing, viral antigen testing, viral nucleic acid testing or viral culture.

The Centre for Disease Control (CDC) definition for diagnosing HIV infection for children under 18 months of age is based on viral detection assays or on clinical criteria

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that include opportunistic infections.[4] In developing countries the antibody measurement is the most widely used technique but is of limited value in the first 15 to18 months of life due to passive transfer of maternal antibodies. The CDC definition is not applicable either because of lack of resources for either viral detection assays or for making clinical diagnosis of opportunistic infections. To overcome these limitations and provide a standardised basis for diagnosing HIV infection in children in developing countries the WHO produced a definition[5] based on a set of clinical signs categorised into major and minor. In order to improve the sensitivity and positive predictive value the case definition was later modified to include persistent or severe lower respiratory tract infection as a major sign.

Lepage *et al* [6] have further simplified the case definition to acute lower respiratory infection and generalised lymphadenopathy. This simple definition was found to have better sensitivity, specificity and positive predictive value compared to the WHO clinical case definition for paediatric AIDS.

In documenting features of children with symptomatic HIV infection in this centre, Nkrumah *et al.*[7] reported generalised lymphadenopathy to be the commonest presentation. Other common features were hepatomegaly, splenomegaly and oral candidiasis.

In this study the criteria for diagnosing HIV infection in infants was the presence of generalised lymphadenopathy with hepatosplenomegaly, oral candidiasis and a strongly positive HIV antibodies by enzyme-linked immunosorbent assay.

HIV Related Respiratory Infections.

A significant cause of hospital admissions and deaths in patients with HIV infection in Africa are respiratory infections. Common bacterial infections are *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus* and *M.tuberculosis*.[8,9] These are the same pathogens that commonly cause pneumonia in the immunocompetent patients. *Pneumocystis carinii* which is a common pathogen causing pneumonia in HIV infected patients in industralised countries[10,11] has been reported less commonly in Africa.[12-14]

The reason for this variability is uncertain but could be due to several factors from under-reporting to under-diagnosis or geographic variability.[15]

National Treatment Guidelines.

The mainstay of management of children with respiratory infections are antimicrobials. In an effort to provide a rational approach to the management of respiratory infections the Ministry of Health of Zimbabwe has developed treatment guidelines as in the EDLIZ.[16]

The recommended first line treatment in infants with severe HIV related pneumonia in the EDLIZ is benzylpenicillin plus gentamycin or kanamycin.[16] Such a recommendation is empirical and based on the spectrum of common pathogens causing pneumonia in patients with HIV infection in developing countries.

Study Objectives.

The objectives of this study were :

1. To describe the characteristics of infants with HIV related pneumonia admitted into two main teaching hospitals.
2. To describe the antibiotic prescribing pattern of health workers for severe HIV related pneumonia in the two hospitals.
3. To assess compliance of health care workers with national treatment guidelines for severe pneumonia in children with HIV infection.

Materials and Methods

The study was conducted in the paediatric medical wards of the two main referral hospitals, Harare Central hospital and Parirenyatwa Hospital which are in the capital city. These are University Teaching Hospitals and get referrals from municipal clinics and health centres from the provinces.

The study population were children one month and above admitted for over 48 hours during the two months May and June 1997, with the following characteristics:

1. Admitting diagnosis of severe pneumonia using the WHO definition.[17]
2. Have clinical features of HIV infection in the presence of repeated strongly positive serology by enzyme-linked immunosorbent assay test by Abbot Laboratories.

Sampling.

The one hundred records of patients with the above eligibility criteria were collected by simple random method from the discharge registers of the two hospitals, Harare (n=49) and Parirenyatwa hospital (n=51). During the same period there were 776 patients aged zero to eight years admitted to Harare Hospital and a total of 326 patients aged zero to12 years admitted to Parirenyatwa Hospital.

Data.

In order to describe the patients' characteristics, the following variables were retrieved from patients' records: age; sex; hospital; nutritional status; duration of hospital stay,; mortality and antibiotics prescribed. The data was obtained using a precoded data collection form and entered by a trained research assistant. In addition all records were reviewed by the Principal Investigator.

The standard treatment guidelines in the national policy document EDLIZ were used to assess prescribing adherence.

Analysis of Data.

The analysis was performed by using Epi Info 6 (CDC Atlanta, Georgia) and Stata statistical packages. Characteristics of patients and treatment variables were compared between the two hospitals and were also compared between patients who died and those who survived.

To compare means the student's t-test was used or its non-parametric equivalent (Kruskal-Wallis) if data were

skewed. For categorical data the Chi squared test was used to compare differences in proportions between two groups. Stepwise logistic regression models were used to determine factors independently associated with mortality. Wald tests were used to determine statistical significance of variables.

Tests of significance at $p< 0.05$ were used to determine statistical significance.

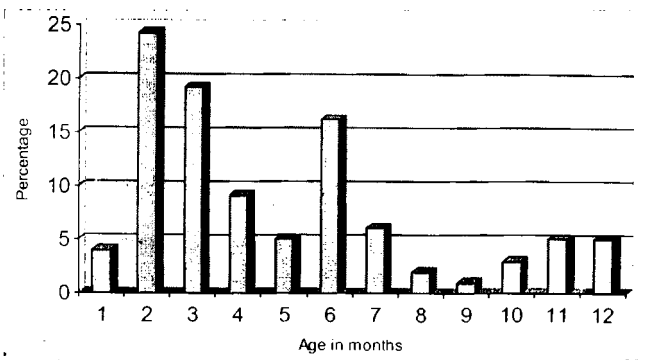
Results

Age Distribution.

Over a period of eight weeks in, May and June 1997 the hospital records of 100 patients aged one to12 months admitted to the two teaching hospitals Harare and Parirenyatwa were analysed. The male: female ratio was 0.94.

There were 49 patients at Harare Hospital and 51 at Parirenyatwa Hospital. Figure I shows the distribution of the age in months, of infants admitted. Seventy seven percent of the patients admitted were in the first six months of life. The peak age was two months and the median was four months (Q1 = 2, Q_3 = 6). The median age of children admitted to Parirenyatwa hospital was 5.5 months (Q_1 = 3, Q_3 = 7) and in Harare Hospital it was 3.0 months (Q1 = 2, Q_3 =6). The difference was statistically significant, p = 0.035.

Figure I: Age distribution in months (n=99).



Duration of Hospital Stay.

The median duration of hospital stay was six days (Q_1 = 4, Q_3 =10). The median duration of hospital stay for Parirenyatwa hospital was seven days (Q1 = 5 Q3 = 11) and that for Harare hospital was six days (Q_1 = 4, Q_3 = 8). The difference was not statistically significant, p=0.075.

Nutritional Status.

The nutritional status of the patients was assessed using the Wellcome Classification[18] (Table I).

Table I: Nutritional status (n=94).

Nutritional Status	Frequency	%
Well nourished	50	53.2
Under weight	36	38.3
Marasmic	8	8.5

Nutritional status was recorded in 94 patients. Only 53.2% of the patients were well nourished, 38.3% were underweight, 8.5% marasmic and none had kwashiorkor. When stratified by age groups as shown in Table II, children below six months had a significantly better nutritional status compared to children over six months $p < 0.001$.

Overall there was no difference in the nutritional status between patients admitted to Parirenyatwa or Harare Hospital, p= 0.514.

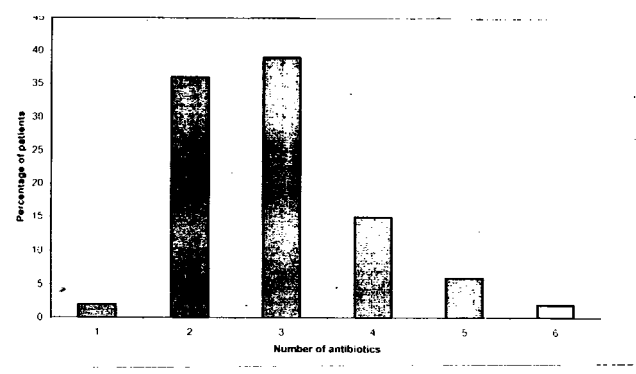
Table II: Nutritional status according to age group (n=94).

Age Group	Good	<80% standard	<60% standard	Total
0-6 months	45 (63.4%)	23 (32.4%)	3 (4.2%)	71
7-12 months	5 (21.7%)	13 (56.2%)	5 (21.7%)	23
Total	50	36	8	94

Drug Use.

The patients admitted received a total of 293 prescriptions of various combinations with an average of 2.9 drugs per patient during the hospital stay. The least number of drugs received was one and the maximum was six per patient. Drugs were changed or added because of lack of clinical improvement in the patients. None of the patients had microbiological evidence as a basis for either initiating the drug treatment or change of treatment. The number of drugs per patient is shown in Figure II .

Figure II: Number of antibiotics prescribed per patient (n=293).



Antibacterial Use.

The various antibacterial drugs used and the frequency are shown in Table III.

The 293 prescriptions constituted 12 different kinds of antibacterial drugs. All drugs were given parenterally except cotrimoxazole, Erythromycin and the anti-tuberculous medication.

The four commonest drugs used, were gentamycin , benzylpenicillin, cotrimoxazole and ampicillin. Ampicillin was used when benzylpenicillin was not available. These four drugs which formed 81.2% of all antibacterials prescribed were used in the following combinations of

Table III: Frequency of antibacterial use.

Antibacterial Agent	Percent of Patients (n=100)	% of all Drugs Used (n=293)
Gentamycin	86.0	29.4
Benzylpenicillin	53.0	18.7
Cotrimoxazole	54.0	18.4
Ampicillin	43.0	14.6
Cloxacillin	14.0	4.7
Chloramphenicol	12.0	4.1
Ceftriaxone	11.0	3.8
Isoniazid	4.0	1.4
Rifampicin	4.0	1.4
Pyrazinamide	3.0	1.0
Kanamycin	3.0	1.0
Erythromycin	2.0	0.7

gentamycin and benzylpenicillin with or without cotrimoxazole or gentamycin and ampicillin with or without cotrimoxazole.

Comparison of Antibacterial use at Parirenyatwa and Harare Hospital.

Of the total of 293 prescriptions, 125 (42.7%) were used at Harare and 168 (57.3%) were used at Parirenyatwa. The average number of drugs used at Harare was 2.5 and at Parirenyatwa it was 3.3. Table IV shows the drugs used at the two hospitals.

Table IV: Use of commonly prescribed drugs in both hospitals.

Drugs	Harare Hosp.	Pari. Hosp.	X^2	df	p value
Benzylpen	12%	92%	64.06	1	<0.001
Cotrimoxazole	43%	65%	5.34	1	0.02
Ampicillin	84%	4%	63.02	1	<0.01
Gentamycin	90%	82%	0.73	1	0.393
Cloxacillin	8%	27%	6.55	1	0.011

Benzyl penicillin, cotrimoxazole and cloxacillin were used more frequently at Parirenyatwa compared to Harare Hospital $p< 0.001$, 0.021 and 0.011 respectively, whereas ampicillin was used more frequently at Harare Hospital, $p = 0.001$. There was no statistically significant difference in the use of gentamycin between the two hospitals, $p= 0.393$.

Anti-tuberculous Drugs.

Four patients had anti-tuberculous drugs. All four patients had other antibiotics in addition. Two had benzylpenicillin, gentamycin and cotrimoxazole. A third patient had benzylpenicillin and gentamycin and the fourth had benzylpenicillin and cotrimoxazole.

Mortality.

Of the 100 patients studied 27 died giving an overall mortality rate of 27.0%.

The mortality rate in Harare hospital was 40.4% which was significantly more than the mortality rate at Parirenyatwa which was 15.7%, OR : 3.69 (95% CI = 1.42 to 9.61; p= 0.005). There was no statistically significant difference in age, sex, duration in hospital stay and nutritional status between those who died and those who survived.

Risk Factors for Mortality.

Step-wise logistic regression analysis was carried out to determine significant factors associated with mortality as shown in Table V.

Table V: Risk factors for mortality using logistic regression analysis.

Factor	Odds Ratio	(95% CI)	Wald Test	p value
Benzylpen	0.32	(0.12-0.82)	-2.4	0.017
Ampicillin	3.04	(1.2-7.7)	2.3	0.019
Hospital	3.7	(1.4-9.6)	2.7	0.007

Children admitted to Harare Hospital were 3.69 times more likely to die compared to children admitted to Parirenyatwa hospital. Mortality was 3.04 times higher in children who had ampicillin than in those who did not have it. Patients on benzyl penicillin were 68% less likely to die than those who were not on it.

Discussion

Severe lower respiratory tract infection is a major cause of morbidity and mortality in children with HIV infection.[10] Common pathogens causing infection include bacteria and *Pneumocystis carinii*.[9-10] In developing countries poor resources and lack of facilities to isolate the pathogens, make accurate clinical diagnosis and antibiotic management relatively difficult. Studies have shown lack of accurate diagnosis as a contributory factor to inappropriate prescribing.[19,20] Even in situations where resources are available difficulties in obtaining diagnostic specimens by non invasive means in children are a major factor for lack of laboratory confirmation.[21]

It is therefore imperative that criteria that do not necessarily rely on bacteriological confirmation be explored to arrive at a logical causation of pneumonia in children with HIV infection.

Age of presentation of pneumonia has been found to be more useful as an indicator of the etiology of pneumonia compared to clinical features or even laboratory tests.[22] Rogers[23] in a study on clinical features of HIV related pneumonia in children in the USA found PCP to occur in 72% of children presenting younger than one year compared to older children where the incidence of PCP was only 38%.

Graham et *al*[24] from Malawi in comparing cases of PCP to bacterial pneumonia in children with HIV infection, reported an earlier age of presentation in children with PCP. In this study the peak age of children admitted was two months. Although it is not possible to make any inference regarding etiology, PCP should still be considered as a possibility in a two months old infant presenting with HIV related pneumonia.

The view that PCP is rare in Africans[12-14] needs reviewing in the light of emerging studies indicating that it is a significant cause of pneumonia in children with HIV

infection in developing countries. In Malawi PCP is responsible for one third of pneumonia mortality in children.[24] In Zimbabwe, necropsy findings in children with HIV infection showed an incidence of PCP to be 16%.[25]

In children with HIV infection, the diagnosis of PCP is based on clinical presentation including age at risk of PCP.[26] Treatment with TMP/SMX (Cotrimoxazole) is instituted presumptively without waiting for diagnostic confirmation.[26]

In Zimbabwe, where diagnostic facilities are not readily available, the recommended treatment for infants with HIV infection presenting with severe pneumonia is a combination of two antibiotics, parenteral penicillin and aminoglycoside.[16] This regimen is directed at treating common bacterial infections.

In this study 54.0% of cases received penicillin, aminoglycoside and cotrimoxazole .

More patients in Parirenyatwa Hospital, 64.7% received cotrimoxazole compared to Harare Hospital 42.8.0%.

Overall only 30.0% of prescriptions followed EDLIZ recommendations where two drugs, penicillin and aminoglycoside were given for treatment of severe pneumonia in children with HIV infection.

A main factor for deviation from standard treatment guidelines was the addition of cotrimoxazole to penicillin and aminoglycoside which are the two recommended antibiotics in EDLIZ for the treatment of severe pneumonia. This regimen of combining treatment for bacterial pneumonia with treatment for PCP in infants presenting with HIV related pneumonia reflects the difficulties faced by medical practitioners in distinguishing the accurate cause of the pneumonia in these infants. This difficulty in distinguishing if the pneumonia is due to bacterial pneumonia or PCP has implications on the long term management of these infants in terms of criteria on which to base decisions for PCP prophylaxis. Combining treatment for both conditions also has cost implications.

Mortality.

It is not possible from the findings of this study to explain the reasons for the higher mortality in Harare Hospital compared to Parirenyatwa Hospital. The two factors which were significantly different in the two hospitals were the age of admission and prescribing pattern. In Harare Hospital the median age of admission was three months compared to 5.5 months at Parirenyatwa Hospital. Although young age is a risk factor for mortality in infants with pneumonia[27] in this study age was not significantly associated with mortality.

Benzylpenicillin, cotrimoxazole and cloxacillin were prescribed more frequently at Parirenyatwa compared to Harare. The only drug that was significantly associated with mortality was ampicillin. Ampicillin was prescribed more at Harare Hospital where benzylpenicillin was not readily available at the time of the study. It is not possible to base the difference in mortality between the two hospitals on the use of ampicillin. There were several factors that could have contributed to the difference in mortality that were not addressed, such as stage of disease presentation, workload and overcrowding.

This study highlights two main findings; the young age of presentation of infants with HIV related pneumonia and the lack of adherence to standard treatment guidelines in the management of these infants.

The difficulties in establishing the cause of the pneumonia in infants with HIV infection was a contributory factor to lack of adherence to standard treatment guidelines. In countries with a high prevalence of HIV infection and with limited resources, a clinical case definition for PCP is required as a measure to provide treatment for infants with HIV related pneumonia, which is evidence based. This approach will also promote rational antibiotic prescribing and will contain cost.

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