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PATTERN OF PATHOGENS IN EAR DISCHARGE OF HIV- INFECTED CHILDREN IN NNEWI, SOUTHEAST NIGERIA

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ABSTRACT

Objective: This is a descriptive, prospective, hospital-based study designed to determine the prevalent organisms in ear infections and their antimicrobial susceptibility patterns in HIV-infected children compared to age- and sex-matched HIV sero-negative patients.

Method: Two hundred and fifty eight HIV-infected children being followed up at the Paediatric HIV clinic had their ears examined for middle ear infection. All those with discharging ears had swabs taken. Culture and antimicrobial sensitivities were ascertained. The same was done for another cohort of 57 age-and sex-matched HIV-negative patients with discharging ears.

Results: Twenty eight (10.9%) of 258 HIV-infected children had discharging ears and were made up of 13 females and 15 males aged between 7 and 132 months. Out of this number 85.7% had chronically discharging ears. 96.4% of the 28 children acquired the HIV infection vertically. 78.6% had been on antiretroviral drugs from one to twenty-one months. 67.9% of the patients had associated opportunistic infections. Acute ear infections were predominant among the control group. *Klebsiella*, *Proteus*, *Staphylococcus* and *Pseudomonas* were major pathogens isolated among the HIV-infected group and *Streptococcus*, *Klebsiella* and *Pseudomonas* for the HIV-negative group. A hundred percent sensitivity was recorded among the quinolones for all bacterial organisms isolated.

Conclusion: HIV-infected children tend to have more of chronic than acute ear infections and this is reflected in the causative organisms. Similar antimicrobial sensitivity patterns apply to HIV-infected and HIV-negative children. There is a need to revisit the use of quinolones in children.

Key Words: Ear Infection, HIV, Children. *(Accepted 13 August 2006)*

BACKGROUND

Human immunodeficiency virus (HIV) infection continues to be a vexing problem in the paediatric population. Otitis media, a common entity in immunocompetent as well as immunocompromised children, is prevalent in paediatric patients with HIV infection.[1, 2] Recurrent infections and complications secondary to otitis media are also common in this population.[3]

Suppurative otitis media is more common in HIV-infected children in the first year of life. By age 3 years, most HIV-infected children will have had one or more episodes of acute otitis media. Signs and symptoms are similar to those in other children. Chronic suppurative otitis media occurs with increased frequency in HIV-infected children and is associated with painless, chronic ear discharge and a perforated ear drum.

Studies from centers in Nigeria [4-7] and other countries in Africa,[8-11] implicate *Staphylococcus aureus*, *Streptococcus pneumonia* and *Haemophilus influenzae* among other isolates in acute otitis media, while *Pseudomonas species*, *Proteus* and *Staphylococcus aureus* were responsible for chronic otitis media

INTRODUCTION

Middle ear infections (otitis media) are the second most common disease of childhood, after upper respiratory infections.[12] Acute otitis media is a recurrent disease, more than one third of children experiencing six or more episodes of acute otitis media by age seven years.[12] This disease is common in children due to their shorter and more horizontal Eustachian tubes, with smaller orifices, and less supporting cartilage when compared to those of

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Adults Mucosal inflammation and oedema due to viral upper respiratory infection further impair middle ear drainage and interfere with host defenses. These cumulatively predispose children to developing acute otitis media.[13] Chronic suppurative otitis media is a chronic inflammation of the middle ear that persists for at least 6 weeks. Both types of otitis media may be associated with otorrhoea through a perforated tympanic membrane.

Early B-cell antibody dysfunction disproportionately affects children who have not generated a repertoire of antibodies protective against common bacteria before onset of HIV-induced helper T-cell dysfunction.[14] Consequently, recurrent infections such as otitis media, sinusitis and pneumonia caused by bacteria like *Streptococcus pneumonia*, *Haemophilus influenzae*, *Staphylococcus aureus*, have been reported as characteristic of paediatric HIV disease.[15]

Neutropenia, caused by HIV infection or antiviral therapy, may also produce mucositis, causing Eustachian tube dysfunction. Likewise, pharyngeal lymphoid hyperplasia associated with HIV infection, may extrinsically obstruct or infiltrate the Eustachian tube.[16] Abnormal local and systemic immunity, characteristic of advanced HIV infection, would reasonably be considered to account, at least in part, for the predilection to recurrent and persistent otitis media among children with symptomatic HIV infection.

Barnett et al [17] reported that abnormally low CD4 lymphocyte counts were associated with significantly greater mean numbers of episodes of acute otitis media during the first year of life and an increased risk for recurrent otitis media. Likewise, Chen et al [18] reported that the frequency of recurrent otitis media increased as the clinical and immunologic status of patients with HIV worsened.

This study was therefore designed to

1 Determine the prevalent organisms in ear infections, and their antimicrobial susceptibility patterns in HIV -infected children presenting to Nnamdi Azikiwe University Teaching Hospital, Nnewi, and to

2 Ascertain differences, if any, between the above group of patients and their age- and sex- matched HIV sero-negative counterparts.

SUBJECTS AND METHODS

Two hundred and fifty-eight HIV-infected patients being followed up in the Paediatric HIV clinic of the Nnamdi Azikiwe University Teaching Hospital, Nnewi, were examined for ear infections during the study period (June 1 to December 31, 2005). Twenty-eight had discharging ears and had ear swabs collected from them. Associated data on gender, route of infection, whether on antiretroviral (ARV) drugs, duration and frequency of ear discharge, CD4 count, absolute lymphocyte count and presence of opportunistic infections, were also obtained. Myringotomy was not done.

Concurrently, age- and sex-matched HIV-negative children with discharging ears were also recruited at the ENT clinic as controls (HIV status of patients is routinely obtained, after pre-test counseling, before any surgical procedures are embarked on). These also had ear swabs obtained, in addition to data on age, gender, duration and frequency of ear discharge and absolute lymphocyte count. Consent was sought and obtained from parents and/or guardians before recruitment in the study.

The ear swab specimens were processed and identified using conventional methods. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 were included as control strains. The antimicrobial agents used for susceptibility testing included: ceftazidime (30μg), ciprofloxacin (5μg), sparfloxacin (5μg), ofoxacin (5μg), cefuroxime (30μg), erythromycin (15μg), doxycycline (25μg), pefloxacine (30μg), cefotaxime (30μg), amoxicillin-clavulanic acid (30μg), gentamicin (10μg), and chloramphenicol. All were oxoid products.

Antimicrobial susceptibility testing was done by the disk diffusion method on Mueller-Hinton agar (Difco laboratories, Detroit Michigan). The inoculum's turbidity was standardized to 0.5 MacFarland standards. Results were interpreted according to NCCLS criteria.[19]

Statistical analysis was done with the SPSS statistical package. The chi-square test was used and the 0.05 level of significance was adopted.

RESULTS

Out of a total of 258 HIV-infected children presenting at the Paediatric HIV clinic during the study period, 28 (10.9%) had discharging ears. They were made up of 13 females (46.4%) and 15 males (53.6%), aged 7 132 months, with an M: F ratio of 1.1: 1. (See Table 1). Twenty-seven (96.4%) acquired the virus vertically and one (3.6%) via blood transfusion.

Twenty-two (78.6%) had been on ARV drugs (for varying durations of one to twenty-one months) in the following combinations: nevirapine, lamivudine and zidovudine (10, 35.7%); nevirapine, lamivudine and stavudine (9, 32.1%); nelfinavir, lamivudine and zidovudine (2, 7.1%); efavirenz, lamivudine and stavudine (1, 3.6%). Six patients (21.4%) were not on any ARV drugs. Nevirapine was initiated at 4mg/kg once daily for the first two weeks, then twice daily at same dose for children above 8 years, while those below 8 years were placed on 7mg/kg twice daily

At same dose for children above 8 years, while those below 8 years were placed on 7mg/kg twice daily after the first two weeks. Lamivudine was given at the dose of 4mg/kg twice daily; Zidovudine 240mg/m^2 body surface area twice daily; Stavudine 1mg/kg twice daily; Nelfinavir 60mg/kg twice daily and Efavirenz for age > 3 years as a single daily dose as follows: 10 - <15kg 200mg, 15 - <20kg 250mg, 20 - <25kg 300mg, 25 - <33kg 350mg and 33 - <40kg 400mg. Twenty-four (85.7%) had chronically discharging ears while 4 (14.3%) had recurrent otitis media. There were associated opportunistic infections in 19 children (67.9%). These included tuberculosis, oral candidiasis, diarrhoeal disease, herpes zoster and facial flat warts.

Table 2 outlines the bacterial organisms isolated from the discharging ears while Table 3 gives the antibiotic sensitivity pattern of isolates from subjects and controls. A hundred percent sensitivity was recorded among the quinolones for all bacterial organisms isolated. All patients received appropriate antimicrobial and ancillary therapies for otitis media. Among the control group 33 (58.0%) had acute otitis media, 21 (36.8%) had chronic otitis media while 3 (5.2%) had recurrent ear infections. It has been suggested that in centers where the CD4 lymphocyte counts cannot be obtained the absolute lymphocyte count could be used as a guide to the level of immunosuppression.[20] Table 4 compared the absolute lymphocyte counts as immunologic categories between test and control subjects. Absolute lymphocyte counts falling within the normal range did not rule out immunosuppression as is shown in Table 5 where the true immunological status as given

Table 1: **Age and sex distribution for cohort and control groups**

Age in months	Males (Test group)	Males (Control group)	Females (Test group)	Females (Control group)
<18	5 (17.9)	6 (10.5)	4 (14.3)	4 (7.0)
18 60	8 (28.6)	11 (19.3)	5 (17.8)	8 (14.0)
>60	2 (7.1)	16 (28.1)	4 (14.3)	12 (21.1)
Total	**15 (53.6)**	**33 (57.9)**	**13 (46.4)**	**24 (42.1)**

Proportions as percentages are in parentheses
p = 0.001737

Table 2: Bacterial isolates from the ears of patients

Organism isolated	No. of Test patients	No. of Control patients
Streptococcus spp	0 (0.0)	31 (53.8)
Klebsiella spp	7 (25.0)	9 (15.4)
Proteus spp	7 (25.0)4	(7.7)
Pseudomonas spp	5 (17.9)	9 (15.4)
Escherichia coli	2 (7.1)	0 (0.0)
Staphylococcus aureus	7 (25.0)	0 (0.0)
No bacterial growth	0 (0.0)	4 (7.7)
Total	**28 (100.0)**	**57 (100.0)**

Table 3: **Antibiotic sensitivity pattern of bacterial isolates from subjects and controls**

Antibiotic	Streptoc-Occus	Klebs-iella	Proteus-s	E.coli	Pseud-omona	Staph aureus
Ceftazidime	-	-	-	-	-	-
Ciprofloxacin	100.0	100.0	100.0	100.0	100.0	100.0
Ofloxacin	100.0	100.0	100.0	100.0	100.0	100.0
Sparfloxacin	100.0	100.0	100.0	100.0	100.0	100.0
Cefuroxime	-	-	-	-	-	-
Erythromycin	75.0	28.6	-	-	50.0	66.7
Doxycycline	-	28.6	33.3	-	-	-
Pefloxacine	-	-	-	100.0	-	33.3
Cefotaxime	-	-	-	-	-	-
Co-amoxiclav	-	-	-	-	-	-
Genticin	-	14.3	33.3	100.0	-	66.7
Chloramphenicol	-	14.3	-	-	-	-
Amoxicillin	-	14.3	-	100.0	-	-
Cotrimoxazole	-	-	33.3	-	-	33.3
Cephalexin	-	-	-	-	-	33.3
Clindamycin	-	14.3	-	-	-	66.7
Streptomycin	-	14.3	-	-	-	33.3
Rifampicin	50	-	-	-	-	33.3

Proportions are percentages of cultures where the drug is sensitive
'-'connotes not tested or resistant

Table 4: **Comparison of lymphocyte counts**

Total lymphocyte count [cells/μL]	No. of children aged < 18 months Months	No. of children aged 18-60 months	No. Of children aged > 60 months
>3500 Not immunosuppressed	**Test** 9 (31.6) **Control** 6(57.1)		
<3500 Immunosuppressed	**Test 1 (5.2)** **Control** 4 (42.9)		
>2300 Not Immunosuppressed		**Test** 12 (42.1) **Control** 15 (80.0)	
<2300 Immunosuppressed		**Test** 0 (0.0) **Control 4** (20.0)	
> 1200 Not immunosuppressed			**Test 6** (21.1) **Control** 35 (90.9)
<1200 Immunosuppressed			**Test 0 (0.0)** **Control 3 (9.1)**

Proportions as percentages are in parentheses

Table 5: Immune status of the cohort under study according to their CD4 counts and percentages

Immune status	Age up to 12 Months	Age 13 59 months months	Age 60 months and over
Not significant immunosuppression	0 (0.0)	0 (0.0)	0 (0.0)
Mild immunosuppression	0 (0.0)	0 (0.0)	0 (0.0)
Advanced immunosuppression	1 (3.6)	6 (21.4)	1 (3.6)
Severe Immunosuppression	7 (25.0)	9 (32.1)	4 (14.3)
Total	**8**	**15**	**5**

Proportions as percentages are in parentheses

DISCUSSION

Recurrent or persistent otitis media is one of the recognized features of HIV infection in children.[20, 21] This is consequent on the attendant immune suppression encountered in HIV infection.[1, 2, 22] In the study 10.9% of 258 HIV infected children presented with recurrent/persistently discharging ears. This finding has been documented in a previous work done in the same hospital.[23] The figure of 10.9% is low compared to other studies.[24, 25] This might probably be due to the fact that myringotomy was not performed in these patients under review and cultures were obtained only from patients with discharging ears.The microbiology of acute otitis media in children infected with HIV is similar to the microbiology of acute otitis media in normal children.[1, 3, 16] Compared to the control patients, the HIV-infected children presented more with chronic otitis media. This was reflected in the organisms isolated from the ear swabs, with a predominance of *Klebsiella spp*, *Proteus spp*, *Staphylococcus aureus* and *Pseudomonas spp*. Their HIV-negative counterparts with a preponderance of acute otitis media, followed by the chronic form, had a yield mainly of *Streptococcus spp*, with fewer *Klebsiella* and *Pseudomonas spp*. *Staphylococcus aureus* is significantly more frequent in otitis media diagnosed in severely immunosuppressed stages of infection with HIV.[16] It has been observed that chronic suppurative otitis media characterized by persistent otorrhoea through a perforated tympanic membrane, is usually attributable to *Pseudomonas aeruginosa*, staphylococci or *Proteus spp*.[16, 26 - 29] All the bacterial isolates were fully sensitive to the Quinolones.

. High sensitivity to quinolones was noted in other studies.[5, 7, 29] Another study in this environment also buttresses this observation.[30] Even though the quinolones have restricted use in paediatric practice trials of their use in treatment of otitis media have been made.[31 - 32]Only *Escherichia coli* was still sensitive to various classes of antibiotics. This obviously makes the choice of appropriate antimicrobial therapy
Problematic.

A comparative analysis of the absolute lymphocyte counts of both cohorts of patients was made with a view to using the lymphocyte count as a measure of immunosuppression.[20] This, however, could not be validated against the CD4 percent for age gold standard for immunosuppression. This concurs with the recommendation by the current World Health Organization Guidelines for Paediatric antiretroviral therapy[21] to avoid the use of absolute lymphocyte counts in monitoring immunosuppression.

CONCLUSION

HIV-infected children tend to have more of chronic than acute ear infections and this is reflected in the causative organisms. Similar antimicrobial sensitivity patterns apply to HIV- infected and HIV-negative children. There is a need to revisit the use of quinolones in children.

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