Prevalence and Pattern of Infectious (Septic) Arthritis in Immunocompromised Patients in a Tertiary Institution in Southern Nigeria

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ABSTRACT

Background: Infectious (septic) Arthritis in immunocompromised (HIV/AIDS) patients can lead to mortality if not diagnosed early and treated properly. The incidence of this condition across the globe is wide and varied. There is paucity of epidemiologic data in our environment. **Objectives:** The purpose of this study was therefore to evaluate the prevalence and pattern of presentation of infectious (septic) arthritis in our local environment and compare it with the global trend. **Materials and Methods:** Blood samples from 360 HIV/AIDS patients aged 19 to 67years suspected to have infectious (septic) arthritis were analyzed for Full blood count, ESR, CD4 count, and blood culture. Synovial fluid from the involved joint was analyzed for white cell count, microscopy culture and sensitivity, and assay for tuberculosis using the ZN stain technique. Mantoux test was done in those suspected to have tuberculous arthritis. Data were analysed using SPSS version 25. **Results:** Sixteen of the 360 participants had infectious (septic) arthritis involving twenty joints of the appendicular skeleton, and three spinal involvements. 50% of these had acute septic arthritis, 25% had HIV associated arthritis, 12.5% had tuberculosis of the spine, while 6.25% each had tuberculous arthritis, and tuberculous arthritis coexisting with tuberculosis of the spine. 62.5% had staphylococcus aureus, 25% streptococcus pyogenes, while 12.5% were Klebsiella Species. ZN stain was positive in two cases. **Conclusion:** The prevalence of infectious (septic) arthritis in HIV/AIDS immunocompromised patients in our environment was 4.4%. Acute septic arthritis was commonest infectious arthritis in this group of patients with Staphylococcus aureus being the commonest organism isolated. The knee joint was the most commonly affected joint.

Keywords: Acute septic arthritis. HIV associated arthritis. Tuberculous arthritis. Tuberculosis of the spine.

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INTRODUCTION

Infectious (septic) arthritis is inflammation of infectious origin occurring in a native or prosthetic joint, which may be acute or chronic, and may affect one or more joints at the same time.[1] It may be due to bacterial organism when it is properly referred to as acute septic arthritis. It may however be viral, fungal, or even be due to tuberculosis. There is also a variant of infectious arthritis which is seen in HIV/AIDS patients in which there is inflammatory joint pain often in the absence of microorganism and usually responsive to a course of steroid therapy and is referred to as HIV associated arthritis.

Acquired immunodeficiency syndrome is a syndrome of Retro-viral origin characterized by profound immune depression resulting in opportunistic infections.[2] Infectious arthritis is thought to be more common in patients with HIV/AIDS due to the background immunosuppression, or additional risk factors such as intravenous drug use, hemophilia, and multiple blood transfusion.[3] The burden of HIV/AIDS in sub-Saharan Africa is high with about 24.7million of the world burden living in the sub-region in 2013.[4] The prevalence rate at Benin City is put at 3.8%, while the National sero-prevalence is 3.34%.[5, 6] It is a huge burden on limited medical economy because of its wide and varied clinical manifestations as a result of profound immunosuppression.[7]

Infectious (septic) arthritis is often an orthopedic emergency. When it is not diagnosed and treated early, it may result in complete joint destruction and severe morbidity, or even mortality for the patient.[8] Chronic disability such as painful stiff joint as well as deformity could result in poor quality of life. Death could result from septicemia, septic shock, or multiple organ dysfunction syndrome complicating infectious arthritis. Early diagnosis and proper treatment may result in complete resolution of symptoms and restoration of normal joint function.[9] Human Immunodeficiency virus infectious has also been documented to be associated with a wide range of rheumatological complications.[10] Patients with HIV/AIDS are more likely to have complicated and severe forms of infectious (septic) arthritis which may affect their quality of life even more adversely hence making a documentation of the pattern of infectious arthritis in this patient group of vital importance. It is also the case that this group of patients are commonly seen by internal medicine specialists, and orthopedic referral made only late when severe forms are more likely to have set in.

Therefore the knowledge of the epidemiology of this condition in HIV/AIDS patients will aid in early diagnosis and treatment in order to reduce or prevent complicated forms and the attendant morbidity and mortality. The epidemiology of infectious arthritis in HIV/AIDS patients in our local population is not known or documented. Few studies have focused on infectious arthritis in this group of patients. There are few descriptions in the literature of the infective organisms involved as well as the diagnostic criteria in musculoskeletal infections in this patient group.

This study will evaluate the prevalence and nature of organisms involved, relationship between the CD4 cell count and infectious arthritis, nature of joint aspirates, serological investigations and radiologic investigations; all of which require further investigation especially in our environment. HIV/AIDS may modify the course of infectious arthritis, and severe complicated forms more likely. The challenge of late diagnosis as the orthopedic surgeon may only be consulted late gives further impetus for this study. The authors are not aware of any similar study from our local population on the subject prior to the conclusion of this study.

METHODOLOGY

Approval was obtained from the ethics and research committee of the University of Benin Teaching Hospital, Benin City, Edo State, Nigeria, before the study was commenced.

All HIV/AIDS positive patients seen between August 2016 and September 2017 at the outpatient clinics of the departments of Medicine, Orthopedics and Trauma, as well as the United States President's Emergency Plan for AIDS Relief (PEPFAR) clinics with complaints of joint pains, swelling or deformity, were eligible for inclusion in the study. We also included patients who were on in-patient admission during the study period. Patients with features of Rheumatoid arthritis, Systemic lupus erythematosus, trauma to the joint, co-morbid immunosuppressive conditions such as diabetes or cancer, as well as those on immunosuppressive drugs or prolonged antibiotic therapy were excluded from the study. Informed consent was obtained from all study participants.

A structured interviewer-administered questionnaire was developed and validated by two independent Orthopedic Surgeons for data collection in the study. It was pre-tested among ten participants before being used in the study. The questionnaire was administered in English language, occasionally an interpreter was used to ensure patients understanding before entry is made.

All patients were clinically assessed for general physical health status and wellbeing. Concurrent chronic ill health and other markers of debility were ascertained. The WHO clinical stage of the HIV/AIDS was also assessed and documented. Pain severity was graded using the visual analogue pain score ranging from 0 to 10, where 0 is no pain and 10 the most severe pain. The musculoskeletal system for each patient was evaluated for painful joint swellings, differential warmth, tenderness, painful limitation of motion, and deformity of the joints and spine.

Ten mls of venous blood was drawn under strict aseptic conditions from each patients forearm vein to confirm the HIV status where this was not already done, to determine the full blood count and Erythrocyte Sedimentation Rate, and to determine the CD4 cell count, and for Blood culture.

Two mls of synovial fluid was also obtained by aseptic arthrocentesis and analyzed for the Total white cell count, Microscopy, culture, and sensitivity as well as assay for Tuberculosis using the Ziehl-Neelsen stain for Acid Fast Bacilli (AFB) when there was significant joint effusion. All samples were transported to the laboratory in a cold box. A Mantoux test was done for each patient. Sample was also stained with 10% potassium hydroxide solution and viewed under direct microscope for fungus.

X-rays of the involved joints were done in those suspected to have infectious (septic) arthritis. Standard antero-posterior (AP) and lateral view x-rays were done. Joint space widening of greater than 2mm was considered significant. In addition, ultrasonography of the suspected joints was done. The presence of echogenic joint effusion was deemed significant.

Data was analyzed using the Statistical Package for Social Sciences (SPSS) version 25. Continuous variables were analyzed using descriptive statistics. Mean values were compared using Students T test. Categorical variables were compared using the non-parametric Chi-squared test. Significance level was set at $p < 0.05$ at 95% confidence interval

RESULTS

Three hundred and sixty (360) patients whose ages ranged from 19 to 67 years were recruited into the study (figure 1). The study population was made up of 164 (45.6%) males and 196 (54.4%) females. Sixteen (4.4%) patients had infectious (septic) arthritis involving twenty joints of the appendicular skeleton (9 ankles, 11 knees), and 3 spinal involvements, see figure 2. Nine (56.3%) of these were females while 7

Table 1: Summary of Laboratory profile for different types of infectious (septic) arthritis (mean values)

Type of arthritis	WBC (synovial fluid) cells/ml	WBC (blood) cells/L	ESR mm/hour	CD4 count cells/ul	ZN Stain	Mantoux test
Acute septic arthritis	4962	2.75 x 10^9	85.5	50	-	-
HIV associated arthritis	787.5	3.78 x 10^9	42	97.5	-	-
TB arthritis	6100	3.0 x 10^9	94.5	98.5	+ve	-ve
TB spine	-	3.5 x 10^9	74	82.5	-	-

Figure 1: Age distribution of patients with infectious (septic) arthritis.

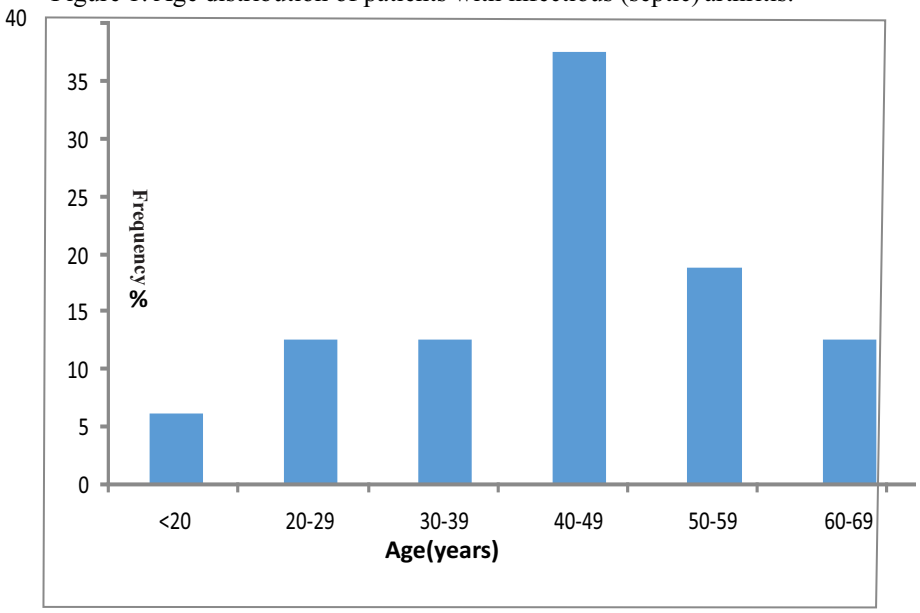


Figure 2: Types of joints involved in infectious arthritis

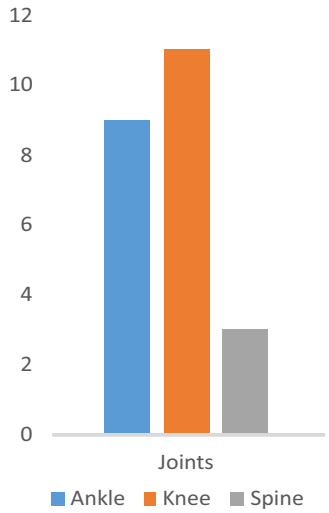


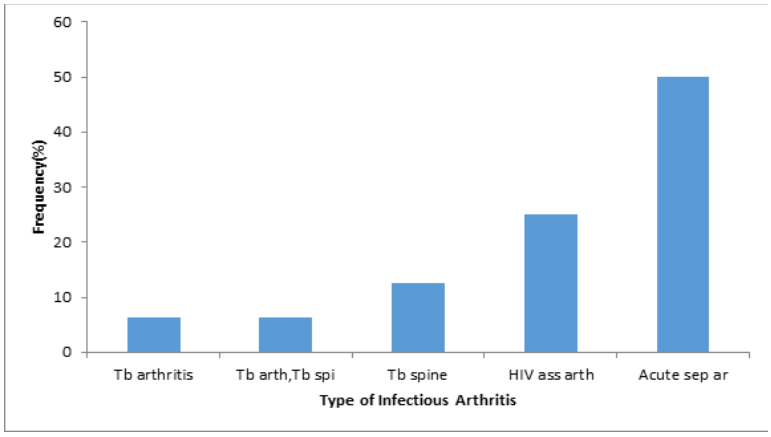
Table 2: Pathogens isolated from the synovial aspirate of those with acute septic arthritis.

Isolated Pathogen	Frequency(n)	Frequency%
Staphylococcus Aureus	5	62.5
Streptococcus Pyogenis	2	25
Klebsiella Spp.	1	12.5
Total	8	100

(43.7%) were males. Eight (50%) of those with infectious arthritis had Acute septic arthritis, four (25%) had HIV associated Arthritis, one (6.25%) had tuberculous Arthritis and another had TB arthritis and TB spine, while two (12.5%) had tuberculosis of the Spine (figure3).

HIV-associated arthritis was diagnosed based on a sterile pattern on synovial fluid analysis with elevated WBC count in contrast to acute septic

Figure 3: Types of infectious arthritis diagnosed among the population



Key: Tb arthritis-Tuberculous arthritis; Tb arth,Tb spine-Tuberculous arthritis and Tuberculosis of the spine; Tb spine-Tuberculosis of the spine; HIV ass arth-HIV associated arthritis; Acute sep ar-Acute septic Arthritis

arthritis[11]

Six of the 8 patients with acute septic arthritis had a mono-articular joint infection (4 involving the ankle joint and 2 involving the knee joint), while 2 had a bilateral ankle involvement. Pain was of severe intensity. The synovial fluid aspirate was purulent and yielded gram-positive organisms in all cases. Staphylococcus aureus was the infecting organism in 5 of the 8 cases, Streptococcus Pyogenes was cultured in 2 cases, while Klebsiella Spp was cultured in 1 case. The mean synovial fluid white cell count was, 4962/ml (see table 1). Full blood count showed mean white cell count [WBC] of 2.75 x 10^9 cells/L, while the mean erythrocyte sedimentation rate (ESR) was 85.5mm/hour. The mean CD4 cell count was 50 cells/ul. There was radiographic joint space narrowing in all, while significant joint effusion was seen on ultrasound.

Four patients with HIV associated arthritis had sub-acute joint pain of moderate intensity involving both knees. Two of this group were on Highly Active antiretroviral Therapy (HAART) prior to presentation. Synovial fluid aspirate was straw colored in this group and yielded no organisms. The mean synovial white cell count was 787.5 cells/ml. Full blood count revealed mean white cell count of 3.78 x 10^9cell/L while the mean ESR was 42 mm/hr, and the mean CD4 cell count was 97.5 cells/ul. There was no radiographic or ultrasonography changes in this group.

One patient had tuberculous arthritis of the left knee alone while another had tuberculous arthritis of the ankle as well as tuberculosis of the spine. Joint pain was of severe intensity. The synovial fluid aspirate was cloudy with a mean WBC count of 6100 cells/ml. ZN staining was positive for AFB, and the Mantoux test was negative. Full blood count showed a mean WBC of 3.0 x 10^9 cells/L, a mean ESR of 94.5 mm/hr, and a mean CD4 cell count of 98.5 cells/ul. There was radiographic evidence of joint space destruction and effusion on ultrasound.

Two of the patients had tuberculosis of the spine. Pain was of severe intensity. There was leucopenia with relative lymphocytosis. The mean WBC was 3.5 x 10^9 cells/L. The mean ESR was 74 mm/hr and the mean CD4 count was 82.5 cells/ul. Radiographs showed

wedge collapse of involved vertebra T12-L1. None of the patients was on HAART.

No cases of gonococcal or fungal arthritis were found in this study. A summary of the laboratory parameters for the study subjects is shown in table I and the isolated pathogens in table 2.

DISCUSSION

Among those that have infectious arthritis in this study, 43.7% were males while 56.3% were females. This gives a male to female (m:f) ratio of 1:1.3. This differs with the m:f ratios obtained in some studies done in the western countries, which range from 4:1-25:1[12][13][14] This observation is thought to be because the mode of transmission of HIV is predominantly homosexual in western countries while it is predominantly heterosexual in Africa.[15] Our observation also differs from previous studies on this subject done in Nigeria, which range from 1.5:1-2.9:1[16-19] This observed difference may be due to the fact that all the previous studies were done in predominantly pediatric population whereas our study is on an adult population. Moreover all the previous studies were done in the normal population whereas our study was specific to immunocompromised HIV/AIDS patients. This is however similar to the m:f ratio of 1:1.4 obtained in a similar study done in Rwanda.[20]

Sixteen out of the 360 patients studied constituting a prevalence rate of 4.4% had infectious arthritis p <0.001. This suggests that infectious (septic) arthritis in this patient subgroup is not uncommon being present in one out of every twenty-five patients. This compares well with some similar studies done previously which reported prevalence rates of 0-3%.[21, 22, 23, 24, 25, 26] However, a similar study done in Kenya in 2008 reported a prevalence rate as high as 17.1%. This higher observed prevalence may be due to the fact that none of the patients in this study was on HAART.[27]

The mean CD4 count in this study is 143 cells/ul which is significantly different from the CD4 count of 248.4 cells/ul in those patients who do not have infections arthritis. This may be either that infectious arthritis occurs in this patient group whose CD4 count is below a critical value or that the presence of infectious arthritis in this patient group further depresses an already suppressed immune system. This finding is similar to results obtained in the study by Casado E *et al* where infectious arthritis always occurred in patients when the CD4 cell count was below 200 cells/ul.[28] It was observed by Edwina and Karen that although there seems to be no clear relationship between CD4 count and infectious arthritis, however more opportunistic organisms occur when the CD4 count is less than 200 cells/ul, than when it is greater than 200 cells/ul when the traditional organisms such as Staphylococcus Aureus are seen more.[29] Similarly, U. A. Walker *et al* in their review found that pyogenic organisms predominate at CD4 counts >250 cells/ul, while opportunistic organisms predominate when the CD4 count is <100 cells/ul.[30] We did not isolate opportunistic organisms in this study, and this may be because the average CD4 count in this study is above 100 cells/ul (143 cells/ul).

The white cell count was either low or on the low side of normal, range 1.1 to 4.3 x 10^9 cells/L in all patients with infectious arthritis. This may be due to the immune-compromised state thus they are unable to mount appropriate response to microbial insults. The mean of 2.75 x 10^9 cells/L observed in those who have acute septic arthritis seems to suggest a more profound immune-suppression than among those with HIV associated arthritis where it was 3.78 x 10^9 cells/L. This may be because HIV associated arthritis is thought to be inflammatory rather than infective in origin. Leucopenia was also the finding in a similar study done by Barziliai A *et al*.[31]

The ESR was elevated in all patients with infectious arthritis where the mean ESR is 75 mm/hr as against a mean value of 45 mm/hr in those without infectious arthritis.

Synovial fluid analysis yielded Staphylococcus Aureus as the most common isolate (62.5%) followed by streptococcus pyogenes (25%) in this study. This agrees with the findings made by Zalavran CG et al and Casado E *et al* in similar studies where Stapylococcus aureus was the most commonly isolated pathogen from the synovial aspirate.[32, 28] This however is in contrast with the findings made by Saraux A *et al* where Streptococcus Pneumonia and Neisseria gonorrhea were the most common pathogens isolated from the synovial aspirates culture and also with Gilks *et al* who found Pneumococcal and Salmonella arthritis more common.[33,34]

We found no case of gonococcal or fungal arthritis in this study. Similarly Zalavran CG *et al* found no fungal arthritis in their study.[32] Barziliai A *et al* found fungal arthritis among a subset of their patients who used intravenous drugs.[31] None of our patients agreed to have used any intravenous drug. Saraux A *et al* found Neisseria gonorrhea as one of the most common isolates in their series.[33] Rasha Maharaj and Girish Mody reported only 2 cases of gonococcal arthritis in their series. They concluded that although gonococcal arthritis may be seen among HIV positive patients, however the disseminated form of gonococcal arthritis is rare in this patient group.[35]

The knee joint was the most commonly involved joint in this study, in keeping with the findings of Saraux *et al* and Zalavran *et al*.[32-33] Bilateral involvement was also common in this study than in other studies: all 4 patients who had HIV associated arthritis had bilateral knee involvement, and 2 of the 8 cases that had septic arthritis had bilateral ankle involvement. There was no case involving the hip or shoulder in this study, and there was no case of poly-articular involvement. This may be because the hip, shoulder, and joints of the upper limb are more commonly involved in patients below 15 years.[16-19,24, 36]

Limitations

This study had some limitations. Some patients did not give consent to be recruited into the study due to traditional attitudes and beliefs about HIV/AIDS and its social stigmatization. This might have affected the outcome. We also did not do histology in this study, especially for those suspected of having tuberculous arthritis which could have improved the yield and might have ultimately affected the pattern of infectious arthritis we obtained in this study.

It is also necessary to establish conclusively whether the low CD4 count observed in patients with infectious (septic) arthritis is as a result of the septic arthritis or a predisposition in this group of patients to infectious (septic) arthritis.

CONCLUSION

The prevalence rate found for infectious (septic) arthritis among HIV/AIDS patients in our population was 4.4%. Females were more commonly affected, and the age group 40-49 years were most affected. Staphylococcus Aureus was the most implicated pathogen, and half of the cases were acute septic arthritis. The knee joint was the most affected joint, and this was often bilateral. There were no cases of fungal or gonococcal arthritis and ESR was significantly elevated in all patients, with a mean value of 75mm/hr and the CD4 count was significantly lowered, with a mean value of 143 cells/ul.

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