Septic Arthritis in Adult Patients at Chris Hani Baragwanath Academic Hospital: A Clinical Audit

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine, Orthopaedic Surgery.

Johannesburg, 2019

Declaration

I, Lerato Ashford Nhlapo declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Orthopaedic Surgery at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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20th……day of …March……2019……in…Johannesburg……

Dedication

This work is dedicated to the women I treasure most in my life:

My wife, Tlotlo.

My mother, Kutlwano.

My daughter, Resego.

Thank you for the boundless love and unending support throughout this journey.

Abstract

As the third-largest hospital in the world, Chris Hani Baragwanath Academic Hospital treats a very large number of patients, many of whom are impoverished, and many who are infected with the Human Immuno-Deficiency Virus (HIV). As a referral centre, a significant number of these patients are afflicted with osteoarticular infection. We wanted to quantify this number and document the clinical, laboratory and microbiological profile of these patients. We retrospectively reviewed almost 200 cases of suspected osteoarticular infections over a four-year period. Seventy-six patients had confirmed bacterial septic arthritis, eleven had confirmed tuberculous arthritis, and there were two cases of fungal septic arthritis. The knee joint was the most commonly involved in all groups. The mean age of all the patients was 42 years (+/- 3years). The male to female ratio was 2:1. *Staphylococcus aureus* was the most common bacterial organism isolated (42%). There was a relatively high prevalence of *Streptococcus pneumoniae* (21%) in our series, most of whom (56%) had concurrent HIV infection. The HIV seroprevalence of the whole group was 51%, with a higher prevalence seen amongst the tuberculous and fungal arthritis groups. There was a statistically significant difference in the white cell count, erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP) levels of the bacterial, tuberculous and negative arthrotomy groups ($p = 0.01$). Bacterial septic arthritis tends to have CRP levels above 100 mg/L and ESR levels between 50 mm/hour and 100 mm/hour. Tuberculous arthritis tends to have CRP levels between 50 mg/L and 100 mg/L, while the ESR tends to be higher than 100 mm/hour. Negative arthrotomies tend to have ESR levels around 50 mm/hour and CRP levels below 50 mg/L. Osteoarticular infection remains a big problem in developing countries, such as South Africa. There is a high rate of HIV co-infection. Uncontrolled diabetes mellitus is also a significant risk factor. Tuberculosis and fungal infections are important considerations in the immuno-compromised patient. Laboratory diagnosis is challenging in adult patients. It appears that 5- to 10-fold increases in CRP and ESR levels (above the normal reference ranges) have a higher positive predictive value for infection, as opposed to inflammatory arthropathies. Future research must incorporate prospective study designs and focus on the value of using other (more sensitive) laboratory tests to make the diagnosis of septic arthritis easier.

Acknowledgements

1. **Supervisor:** Dr. T.I. Sefeane
2. **Research staff at the University of the Witwatersrand Department of Orthopaedic Surgery:** Dr. M. Jingo and Dr. B. Milner
3. **Head of Department of Orthopaedic Surgery, University of the Witwatersrand:** Prof. M.T. Ramokgopa

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Nomenclature

A. baumannii: Acinetobacter baumannii

AIDS: Acquired Immunodeficiency Syndrome

ART: Anti-Retroviral Therapy

CD4: Cluster of Differentiation 4

CNS: *Coagulase Negative Staphylococcus*

CEO: Chief Executive Officer

CHBAH: Chris Hani Baragwanath Academic Hospital

CRP: C-Reactive Protein

E. Coli: *Escherichia coli*

ESR: Erythrocyte Sedimentation Rate

HBA1c: Glycated Haemoglobin

HIV: Human Immunodeficiency Virus

HREC: Human Research Ethics Committee

JWBC: Joint White Blood Count

MTB: *Mycobacterium Tuberculosis*

MTB/RIF: *Mycobacterium Tuberculosis*/Rifampicin assay

NAAT: Nucleic Acid Amplification Test

NHLS: National Health Laboratory Services

NPV: Negative Predictive Value

PCT: Procalcitonin

PPV: Positive Predictive Value

S. agalactiae: *Streptococcus agalactiae*

S. aureus: *Staphylococcus aureus*

S. dysgalactiae: *Streptococcus dysgalactiae*

S. epidermidis: *Streptococcus epidermidis*

S. pneumoniae: *Streptococcus pneumoniae*

S. pyogenes: *Streptococcus pyogenes*

S. marcescens: *Serratia marcescens*

UNAIDS: The Joint United Nations Programme on HIV and AIDS

VL: Viral load

Vs: versus

WCC: White Cell Count

CHAPTER 1

1 Introduction and literature review

1.1 Background

Being the third largest hospital in the world, Chris Hani Baragwanath Academic Hospital (CHBAH) in Soweto has developed a reputation for treating a myriad of ailments in the medical and surgical disciplines. Every year 150,000 inpatient cases and 500,000 outpatient cases are registered.

Our orthopaedic department boasts a comprehensive array of sub-specialities that are equipped to treat a wide range of musculoskeletal conditions. Furthermore, we cater to the needs of not only the greater Soweto region, but through an extensive referral system, we assess patients from as far as our neighbouring countries in Sub-Saharan Africa. This large number of patients presents an opportunity to do meaningful research studies and projects.

Due to the current Human Immuno-Deficiency Virus (HIV) pandemic (and other immune suppressive diseases), we have noticed a rise in the number of infective musculoskeletal conditions. Also, the landscape of musculoskeletal infections appears to be changing, in as far as clinical presentation, severity and pathogenic organisms are concerned.

The goal of this research project was to categorise and document the clinical, biochemical and microbiological profile of patients who were treated at our unit for infective conditions affecting their joints. Secondarily, we wanted to assess the manner in which we diagnose and treat our patients and ensure that this was in line with internationally accepted standards.

The study retrospectively reviewed data as far back as five years ago and analysed clinical profiles and laboratory results of the patients treated for suspected septic arthritis. We hope these data contribute positively to existing literature and help us to improve our service delivery to the CHBAH patient population.

1.2 Literature review

Inflammation of a joint can have a multitude of causes, both acute and chronic. Infective causes can have potentially dire consequences, not only for the involved joint/limb, but also for the patient as a whole.

Septic arthritis is defined as an acute infection of a joint[1], and is one of the recognised rheumatologic and orthopaedic emergencies. In the emergency department, patients present frequently with one (or more) irritable joint(s)[2]. Bacterial septic arthritis is not usually the most typical, but certainly the most serious cause. Irreversible cartilage damage has been shown to occur as early as within eight hours of purulent material accumulating within the joint[1]. As such, delayed diagnosis can result in poor outcomes, and contribute to significant morbidity and mortality (up to 15% in-hospital fatality rate)[3]. This necessitates prompt diagnosis, early administration of intravenous antibiotics and surgical treatment.

1.2.1 Epidemiology

According to a systematic review of the literature by Mathews *et al*., the epidemiology of bacterial septic arthritis is that of a disease that broadly affects the very young, and the very old[2]. In this study, the quoted European incidence ranges from 4 – 10 cases per 100,000 patients per year, with disadvantaged communities having up to 29 cases per 100,000 patients per year[2]. Li *et al*. did a retrospective review of cases from a teaching hospital in New York from 1996 to 2001. Out of 73 patients, their mean age was 51 years old (with 19% of them being over the age of 65). Seventy one percent of the patients were male[4].

In a prospective observational cohort study by Courdec *et al.*, the mean age of the patients was 59.8 years. Fifty nine percent of the patients were male in this study[5].

There is a paucity of South African data regarding the epidemiology of bacterial septic arthritis in the adult population. A study from our centre (CHBAH) by Matekane *et al.*, investigated the microbiology of septic arthritis, and showed that the mean age of the patients was 44 years. In this study, 61% of the patients were aged 26 to 49 years[6]. However, the authors did not mention patient gender in this study.

In a retrospective review of hospital data out of Steve Biko Academic Hospital in Pretoria, Nel *et al*. reported a series of 125 patients over a 46-month period, with ages ranging from 16 to 72 years[7]. Comparing within the African context, in a study coming out of Nigeria, Mue *et al*. reported a series of 35 joints (in 30 patients) over a period of five years[1]. This study also included paediatric patients. In the adults, 36% of them were between the ages of 17 to 60 years. Ten percent of them were above the age of 60.

1.2.2 Joint involvement

Most studies agree that the knee joint is most commonly affected by septic arthritis[8]. The knee is affected 39% – 76% of the time, followed by the hip (20% – 31%). Frequently, simultaneous involvement of more than one joint can occur (up to 20%)[2]. The data from Nel *et al*. showed that knee involvement was 73% in their series[7]. Other studies have also demonstrated similar findings[4,5,9]. The literature also agrees as to which other joints are most commonly involved after the knee. In a ten-year retrospective review, Clerc *et al*. found that the hip joint (17%) and the shoulder joint (16%) were the next most commonly involved after the knee (38%). These numbers are somewhat diluted as the study also included small joints (finger and toe interphalangeal joints). In Pretoria[7] and in West Africa[1], the sequence of joint involvement was the same (knee>hip>shoulder), while joint involvement was not looked into in the most recent study from CHBAH[6].

Multiple joint involvement is observed in approximately 10% to 20% of cases. In these cases, the knee joint is almost invariably involved as well.

1.2.3 Diagnosis

When faced with a patient who presents with a history of an acutely irritable joint, the diagnosis of septic arthritis is often difficult to ascertain. In adults this is further confounded by the presence of pre-existing joint disease, as the symptomatology may be similar. The main aim is to distinguish a septic arthritis from other causes of an acutely irritable joint (e.g. inflammatory arthritis). To do this, clinical features and laboratory investigations are used in conjunction to reach a diagnosis.

In a two-year prospective study, Gupta *et al*. reported a history of fever in approximately a third of cases, sweats in less than 20%, and rigors in less than 10% of cases. Furthermore, a temperature of > 37.5^0C at clinical presentation was present in 60% of cases[9]. Joint pain and tenderness are important clinical features, and have been found to have a sensitivity of 85% – 100% in the diagnosis of septic arthritis[5].

Laboratory investigations complete the armamentarium used to diagnose septic arthritis. Blood White Cell Count (WCC) is usually elevated, along with elevations in serum Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). Li *et al*. retrospectively reviewed the blood results of 73 patients with confirmed bacterial septic arthritis. They found that a raised WBC (> 11,000 cells/mm^3) had a sensitivity of 48%, while a raised ESR (> 30 mm/hr) had a sensitivity of 96%[4]. Courdec *et al*. prospectively followed up 105 patients with suspected septic arthritis (29 of whom were found have a confirmed diagnosis of septic arthritis). In their study, they noted that an ESR higher than 50 mm/hr and a CRP higher than 100 mg/L were more commonly observed in septic arthritis[5].

A systematic review by Magaretten *et al*. noted, that raised WCC, CRP and ESR are of limited diagnostic power. They found that a raised joint White Blood Count (jWBC) was more reliable[3]. They also noted that high quality evidence was lacking, as this systematic review was mainly done from retrospective studies. In a meta-analysis by Carpenter *et al*., they noted that there is no specific cut-off for ESR and CRP that would significantly increase or decrease the post-test probability of septic arthritis, and that synovial fluid analysis for culture and jWBC should always be done[11]. Borzio *et al*. evaluated over 400 knee aspirates and found that just under 5% were confirmed septic arthritis. On comparing the two groups, they found that there was no statistical difference in the WCC and ESR[12]. They also noted that a jWBC higher than 64,000 cells/mm^3 yielded optimum sensitivity and specificity.

Blood cultures are positive in approximately one in four cases, and are the only positive microbial culture in 9% of cases where diagnostic arthrocentesis is performed. Fourteen percent of cases of bacterial septic arthritis are diagnosed on the basis of the blood culture (in the setting of negative joint cultures). Gross examination of joint fluid by a rheumatologist has been reported as 94% sensitive and 58% specific for differentiating inflammatory from non-inflammatory arthritis.[5]

The gold standard in the diagnosis of septic arthritis is a demonstration of positive microbial cultures from joint fluid. In 50% of cases, the Gram stain informs the clinician of the aetiology of the sepsis. Culture improves this figure by two-thirds.

jWBC > 50,000 cells/mm^3 is considered diagnostic of septic arthritis, given that not all joint aspirates will yield a positive culture[2].

A case definition of septic arthritis can be divided into four categories (Modified Newman Criteria):[13]

1. Causative pathogen isolated from the suspected joint.
2. Causative pathogen isolated from a site other than the joint (e.g. blood culture), in cases where the clinical suspicion of a septic arthritis is high.
3. Turbid fluid aspirated or drained from a joint, in the event that the patient has been on antibiotics. Once again, the clinical suspicion of a septic arthritis must be high.
4. Features in keeping with septic arthritis found on histological analysis of the tissue; or post-mortem findings.

1.2.4 Microbiology

Most authors agree that the Gram-positive organism, *Staphylococcus aureus* (*S. aureus*) is the most common causative organism in bacterial septic arthritis[13]. One also must consider mycobacterial and fungal organisms as part of the differential diagnosis in infective causes.

In the series by Gupta *et al.*, 91% of the organisms were *S. aureus* and *streptococcus* combined[9]. Similar results were reported by Li *et al*.[4]. In the series by Matekane *et al*., 55% of the organisms isolated were Gram-positives, 40% were Gram-negatives, and 5% were mycobacterial[6]. In the series by Nel *et al.*, 53% were Gram-positives, and 36% were Gram-negatives[7].

Neisseria gonorrhoeae, a Gram-negative organism mostly encountered in sexually transmitted infections, used to be a prominent causative organism in bacterial septic arthritis. Its prevalence has decreased significantly over the last couple of decades[14].

Streptococcus pneumoniae (*S. pneumoniae*) is a Gram-positive organism that is more prevalent in certain groups (HIV-positive, rheumatoid arthritis, alcoholism, post-splenectomy)[15]. It accounts for 3% to 6% of cases of bacterial septic arthritis, but its prevalence has been on a steady decline. In a five-year retrospective review from Brussels, 3.3% of the cases of septic arthritis were attributable to *S. pneumoniae*. None of the patients in this study were HIV-positive[16]. In another retrospective review from Boston, only 8% of the patients with *S. pneumoniae* septic arthritis were HIV-positive[15].

Tuberculosis (TB) of the peripheral joints is an important consideration in the differential diagnosis of any patient presenting with a suspected septic arthritis. Garrido *et al*. reviewed all cases of peripheral TB over a ten-year period in Madrid. Ten percent of all TB cases involved the musculoskeletal system. Two-thirds of these cases involved the joints, and one-third involved the bones[17]. Furthermore, they found that 90% of cases were mono-articular (of which 30% involved the knee). There was no mention of HIV prevalence in this study. Talbot *et al*. retrospectively reviewed 61 cases of musculoskeletal TB in Bradford, over six years. They found that 48% of the cases involved the spine, 18% involved the upper extremity joints, and 8% involved the knee[18]. None of the patients in this study were HIV-positive. Lertsrisatit *et al.* retrospectively reviewed 27 cases of extraspinal TB in Bangkok, over eight years. They found that one-third of cases involved the wrist, and another one-third involved the knee[19]. Only one of their patients was HIV-positive. Due to the chronic nature of the illness, a delay in a diagnosis is a problem that clinicians face. In the above-mentioned study by Garrido *et al*., 60% of the patients had a delay in diagnosis (from the first symptom) of more than six months[17].

Fungal septic arthritis is rare. It is encountered mostly in patients with significant immune-suppression, although immune-competent individuals are also affected. The most common organisms in fungal musculoskeletal infection are the *Candida* and *Aspergillus* genera[20]. Seventy-five percent of *Candida* septic arthritis involves the knee joint. With regards to *Aspergillus*, Gamaletsou *et al*. retrospectively reviewed 31 cases over 48-years. They reported that 55% of the patients were immunocompromised. Furthermore, 35% of cases involved the knee, and 45% of cases had involvement of two or more joints[21].

1.2.5 HIV and Osteoarticular Infection

As of 2015, the Joint United Nations Programme on HIV and AIDS (UNAIDS) estimates that there are seven-million people in South Africa living with AIDS[22]. Data on the relationship between septic arthritis and HIV are scarce, with most of it coming from Europe and North America. There are few African studies. A study conducted in Rwanda by Saraux *et al*. found that 79% of adult patients with a septic joint were also HIV-positive[23]. They also found that the differences in prevalence among HIV-positive and HIV-negative individuals was not statistically significant. However, compared to a control group, patients with septic arthritis were more likely to be HIV-positive. These data are relatively old (from 1997) and the study population was small (24 patients). According to Mody *et al*., septic arthritis is uncommon in individuals infected with HIV, however, it seems to be more prevalent in developing countries where there are more severe HIV infections[24]. Furthermore, they found that there was no correlation between CD4 count and the frequency of infections.

A study conducted in Italy over a ten-year period found that 0.3% (out of a total of 4,023) of HIV-positive patients developed osteoarticular infection[25]. In another study conducted in Amsterdam, 1.5% of HIV-positive patients (total 1,515) developed osteoarticular infection, over a period of twenty-years[26]. In HIV-positive individuals, one must be cognisant of rheumatological conditions which can mimic a septic arthritis. These conditions include HIV-associated arthritis, reactive arthritis, arthralgia, painful articular syndrome and undifferentiated spondyloarthropathy[27].

1.2.6 Risk factors and other co-morbid conditions

According to Sharff *et al*., the most important risk factor for septic arthritis is abnormal joint architecture, as is seen in rheumatoid arthritis, crystal arthropathies and osteoarthritis[28]. Other important local risk factors to consider are systemic lupus erythematosus (SLE), previous trauma to the joint and previous surgery[14].

Septic arthritis is also more commonly seen in systemic conditions that cause immunosuppression. These conditions include[14]:

- Diabetes Mellitus

- Intravenous drug abusers
- Liver cirrhosis
- End-stage renal disease
- Chronic steroid therapy

Low socio-economic status has also been found to be a significant risk factor for septic arthritis[2].

Margaretten *et al*. also include elderly age (> 80 years old) and HIV infection as significant risk factors for bacterial septic arthritis, although there is a lack of high quality evidence to support these risk factors[3].

It is well-established that immunosuppression, such as that seen in HIV and chronic immunosuppressive therapy (e.g. steroids, chemotherapy), is a significant risk factor for tuberculous arthritis as well as fungal septic arthritis[19,20,21].

Diabetes is associated with up to 22% of bacterial septic arthritis cases, as was seen in a retrospective review by Li *et al*.[4]. Furthermore, it has also been established that poor glycaemic control, as determined by an elevated glycated haemoglobin level (HBA1c), is a risk factor for bacterial infections in diabetics. Hine *et al*. followed up a cohort of diabetic patients over twelve months. They found that there was an overall increased risk (odds ratio = 1.50) of bacterial infections in diabetics, when compared to non-diabetics[29].

As stated earlier, crystal arthropathies (such as gout), have also been noted to be a risk factor for septic arthritis. This presents a diagnostic challenge when the clinician is deciding whether a patient has septic arthritis, or an acute attack of gout. The former requires urgent surgical treatment, whereas the latter can be successfully managed with medication alone. Yu *et al*. reported 30 cases of concomitant gouty and septic arthritis over a fourteen-year period[30]. In this study, they found that 33% of patients were afebrile on presentation to the emergency department. More recently, Prior-Español *et al*. also presented a series of patients with concomitant septic and gouty arthritis. They retrospectively reviewed twenty-five cases, 60% of which were due to *S. aureus* and 12% of which were due to TB[31]. Thus, the clinician needs to have a high index of suspicion when dealing with such patients.

Reactive arthritis also deserves a special mention. The definition of reactive arthritis is an inflammatory arthritis that occurs due to an infection at a distant site[32]. These sites are most commonly in the gastrointestinal tract and genitourinary tract. This causes a rise in inflammatory makers (WCC, ESR, CRP) such as those observed in bacterial septic arthritis and can therefore, cause a diagnostic quandary for the clinician. Furthermore, reactive arthritis is one of the reported rheumatological complications of HIV[24,27], thus compounding the diagnostic challenge in the HIV-positive patient with an acutely irritable joint. Schmitt reports that an important distinguishing factor is the jWBC, which is usually not higher than 50,000 cells/mm^3 (in comparison to the jWBC > 50,000 cells/mm^3 in septic arthritis)[32].

Considering all the above-mentioned issues, the clinician must be well-aware of the considerable challenges involved in diagnosing septic arthritis in the adult patient.

1.3 Study Aim and Objectives

The aim of the study is to ascertain the epidemiological, clinical, biochemical and microbiological profile of adult septic arthritis at CHBAH.

The objectives of this study are to:

- Obtain data of adult patients who underwent joint arthrotomies in emergency theatre for the designated study period.
- Document the co-morbidities of all these patients as:
    - Rheumatoid Arthritis.
    - Diabetes.
    - HIV positive or negative.
        - Known status prior to admission.
            - Taking antiretroviral therapy (ART) or not.
        - Newly diagnosed on admission.
    - Other (e.g. Gout)
- Obtain joint culture results and blood results (including blood cultures) of these patients. The blood results would also include:
    - Glycated haemoglobin level (HBA1c) for the diabetic patients.
    - Serum uric acid level
    - CD4 count and Viral Load (for the HIV positive patients).

CHAPTER 2

2 Methodology

2.1 Research Question

What is epidemiological, clinical, biochemical and microbiological profile of adult patients with septic arthritis at CHBAH?

2.2 Research Design

The study was a retrospective review of theatre data, hospital records and laboratory results. The data were collected for the period 01 January 2013 to 31 July 2017.

2.3 Materials and Methods

- Data were collected from the CHBAH emergency orthopaedic theatre register, looking at all surgical debridements or arthrotomies of large joints.
- The names and hospital numbers of these patients were recorded, and their files collected from records, looking at the following:
    - Co-morbidities, such as diabetes, gout, HIV, rheumatoid arthritis, or "other".
    - Consent for HIV testing was checked, recorded. The process of HIV testing was also done under the tenets of Voluntary Counselling and Testing (VCT), where patients were counselled before and after the test. Those who tested HIV-positive were referred to the infectious diseases physicians for possible initiation of ART.
- To ensure anonymity, all data relating to each patient was captured anonymously on a separate data sheet (see Appendix A). Each patient was given a unique study number. The original data were kept in a separate file.

Blood and culture results were obtained through the National Health Laboratory Service (NHLS) system, specifically looking for:

- White Blood Cell Count (WCC)
- Serum Erythrocyte Sedimentation Rate (ESR)
- Serum C-Reactive Protein (CRP)
- HIV status (if tested); if positive, a CD4 and Viral load was recorded
- Glycated Haemoglobin levels (HBA1c), if diabetic
- Serum uric acid
- Blood cultures
- Joint fluid cultures

A positive case of a septic arthritis was defined according to the modified Newman criteria, as mentioned above (one or more criteria = septic arthritis)[13].

Following the exclusion process, the remaining cases were broadly classified into the following categories:

- Bacterial septic arthritis
    - Confirmed case definition of septic arthritis according to the modified Newman Criteria. The histological findings which confirmed bacterial septic arthritis were those "acute suppurative synovitis".
- Tuberculous arthritis
    - Positive joint culture of *Mycobacterium tuberculosis* (*MTB*).
    - Histological findings suggestive of tuberculosis (i.e. histological findings in keeping with necrotising granulomatous inflammation), in conjunction with raised CRP and ESR.
- Fungal arthritis
    - Positive joint culture of a fungal organism.
- "Negative" arthrotomy
    - Any case which did not fulfil any of the criteria for bacterial septic arthritis, tuberculous arthritis or fungal arthritis.

2.4 Sample

Non-probability sampling methods were used. All the cases of suspected septic arthritis were recorded.

Inclusion criteria:

- Patients 18-years-and older, who had arthrotomies of any large joint(s).
- Complete clinical notes and laboratory results.

Exclusion criteria:

- Patients younger than 18-years-old.
- Penetrating joint trauma.
- Small joint(s) e.g. joints in the hands and feet.
- Prosthetic joints.

2.5 Ethics

Permission to conduct research at CHBAH was obtained from the hospital CEO (see Appendix B). The research protocol was submitted to Human Research Ethics Committee (HREC) (Medical), University of the Witwatersrand for approval prior to data collection. Ethics clearance was granted unconditionally (see Appendix C).

2.6 Data Collection

The data collection was done by the primary investigator. A process was undertaken to read through the physical theatre records and capture the data on the data capturing sheet (shown in Appendix A). The demographic data of the patients, specifically age, gender, site of infection and co-morbid diseases, were documented. Furthermore, the blood results and joint culture results were documented.

2.7 Data Analysis

Data from the data capturing sheet were entered into a Microsoft Excel Spreadsheet. Data from the spreadsheet were analysed using the Stata 14 computer program. The following descriptive statistical methods were used:

- Univariate analysis of categorical and numerical data, looking for measures of central tendency.
- Bivariate analysis of both categorical and numerical data, looking for associations between different variables.

- Student's t-test and ANOVA tests were applied to the numerical data, to ascertain if the differences among groups was statistically significant. A *p*-value < 0.05 was considered statistically significant.

2.8 Limitations

Being a retrospective review, the limitations of this study include:

- A selection bias, in that the patients in the study will most likely be those with already compromised immune systems. Therefore, the prevalence of certain diseases in the study sample may be overstated, as compared to the general population. This may also result in overestimation of diagnostic tests such as sensitivity and specificity (analytical bias).
- Confounding, which may occur due to certain variables (which may affect the outcome) not being recorded or analysed. This may result in inaccurate statistical tests or hypotheses which are done on the available data.
- Inferior level of evidence compared to prospective studies.
- Poor record-keeping in the theatre and hospital records. This could result in incomplete data, such that it is not suitable for statistical analysis. Thus, minimising the effective sample size for statistical analysis and skewing the results.

  Similarly, the true prevalence of co-morbid conditions will not be accurate, as some patients may not have been tested for HIV or any of the other co-morbid conditions.

CHAPTER 3

3 Results

3.1 What is epidemiological, clinical, biochemical and microbiological profile of adult patients with septic arthritis at CHBAH?

During the period 01 January 2013 to 31 July 2017 there were a total of 204 recorded surgical joint arthrotomies in the theatre register. Of all these, 22 were excluded due to not meeting the inclusion criteria (see Table 3.1).

Upon checking the microbiological and biochemical results of the remainder of the patients, 37% (*n* = 68) of them had incomplete results on the laboratory system. This subset of patients was therefore excluded from any further statistical analysis.

Following the exclusion process, the remaining 63% of patients (*n* = 114) had sufficient results to deem them adequate for statistical analysis.

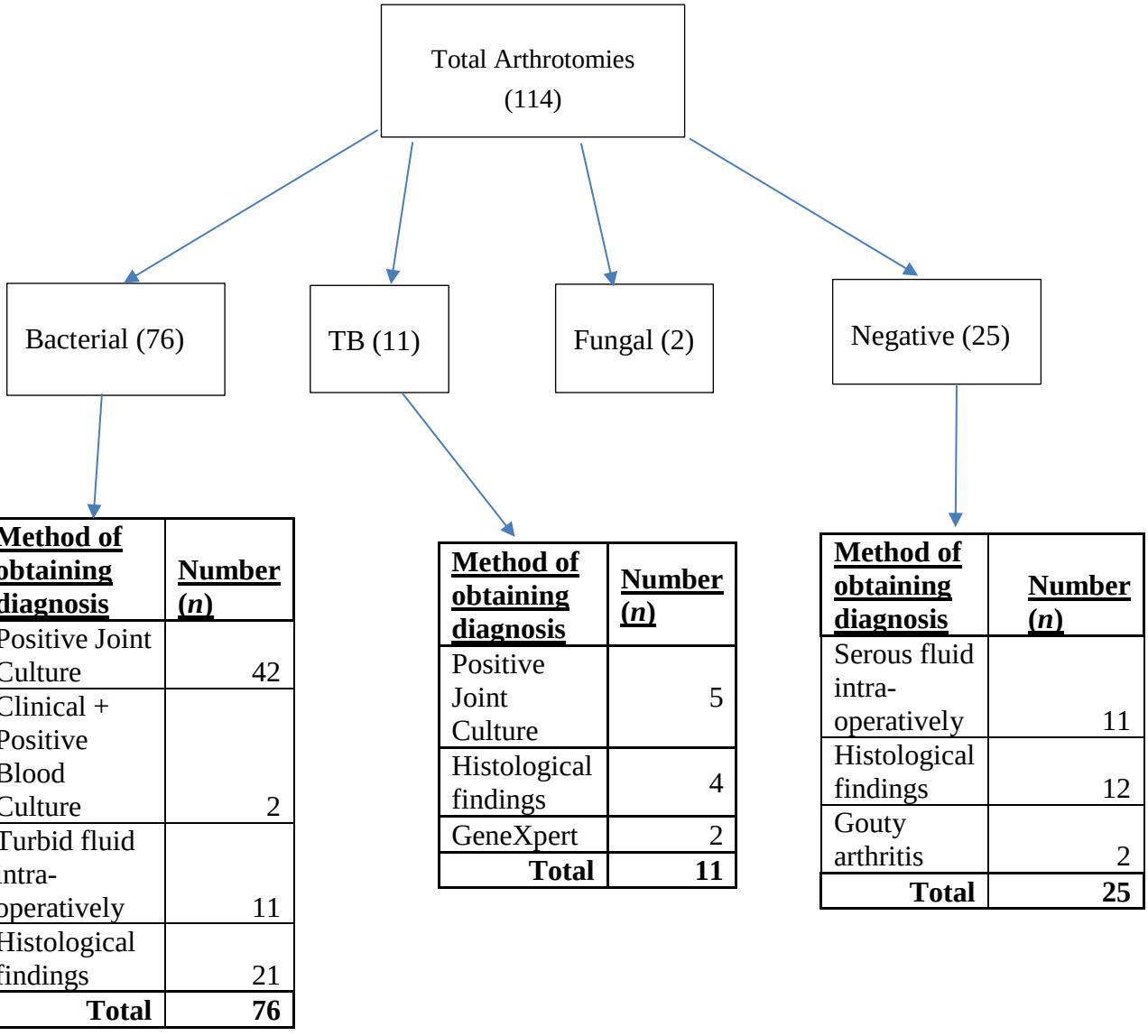
Of these, 76 were diagnosed as having bacterial septic arthritis, 11 had tuberculous arthritis, 2 had fungal arthritis and 25 had negative arthrotomies (see Figure 3.1).

Table 3.1 Summary table of arthrotomies excluded

Reason for exclusion	**Number (*n*)**
Age younger than 18	12
Bursitis/superficial abscess	3
Penetrating joint trauma	6
Small joint(s), e.g. finger	1
TOTAL	**22**

3.1.1 Culture results

Of the 114 cases deemed suitable for statistical analysis, 66.7% (*n* = 76) were bacterial septic arthritis, 9.6% (*n* = 11) were tuberculous arthritis, 1.7% (*n* = 2) were fungal septic arthritis, and 21.9% (*n* = 25) were negative arthrotomies (see Figure 3.1).



Method of obtaining diagnosis	Number (*n*)
Positive Joint Culture	42
Clinical + Positive Blood Culture	2
Turbid fluid intra-operatively	11
Histological findings	21
Total	**76**

Method of obtaining diagnosis	Number (*n*)
Positive Joint Culture	5
Histological findings	4
GeneXpert	2
Total	**11**

Method of obtaining diagnosis	Number (*n*)
Serous fluid intra-operatively	11
Histological findings	12
Gouty arthritis	2
Total	**25**

Figure 3.1 Chart displaying the breakdown of cases deemed suitable for statistical analysis

3.1.1.1 Bacterial septic arthritis

Of the cases of bacterial septic arthritis, the diagnosis was most commonly obtained by positive joint culture (55%) and histological findings (28%). Clinical findings of purulent material in the joint also played a significant role (14%).

Forty-five percent of the joints did not yield a positive culture, and it is in these cases that other means of diagnosis was utilised.

Of the culture-positive cases, the most common organism which was isolated from the joint was *S. aureus*. Other Gram-positive organisms were also relatively common, as depicted in the following pie chart. Gram-negative organisms were not commonly cultured in this series (see Figure 3.2).

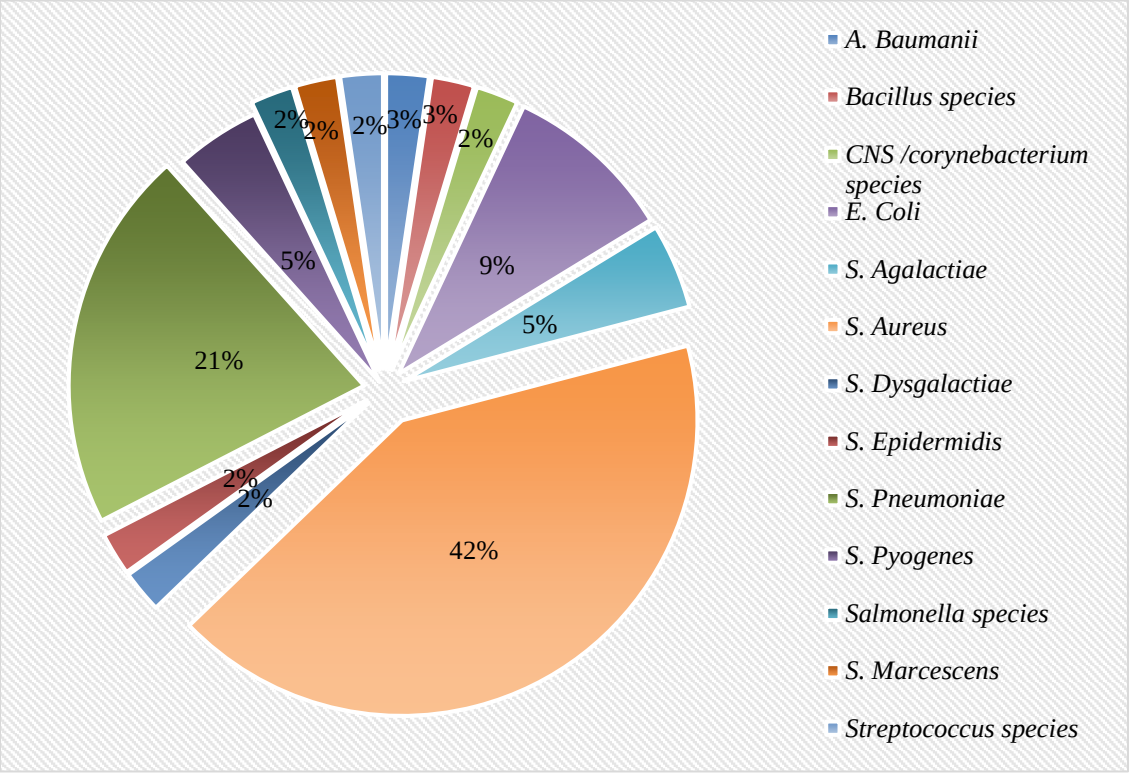


Figure 3.2 Pie chart displaying breakdown of organisms isolated in joint cultures (CNS = *Coagulase Negative Staphylococcus*)

Blood cultures were infrequently requested in this series (66% of patients did not have a blood culture done). Of the patients who had blood cultures taken, there was no organism isolated in 69% (*n* = 18). Of the culture-positive ones, the most common organism isolated from blood was also *S. aureus* (see Figure 3.3).

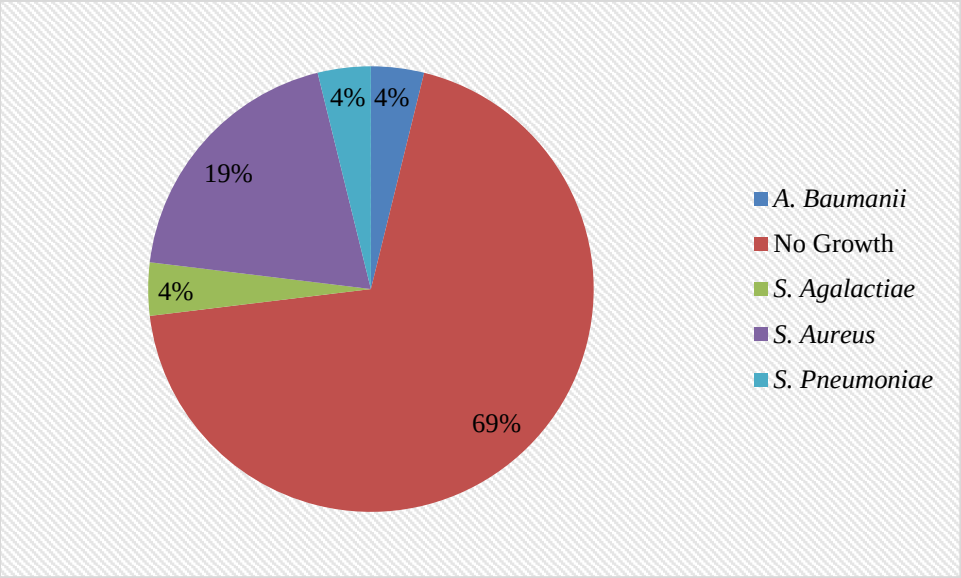


Figure 3.3 Pie chart displaying a breakdown of blood culture results

Simultaneous positive blood culture and positive joint culture was uncommon (*n* = 6). *S. aureus* was most the most common organism (*n* = 4) isolated in this scenario.

3.1.1.2 Tuberculous arthritis

Of the cases of tuberculous arthritis (*n* = 11), the diagnosis was commonly obtained by positive joint culture (45%) and histological findings (36%). The use of nucleic acid amplification tests (NAAT) yielded positive results in 19% of cases.

All cases of positive culture and NAAT yielded *MTB* as the causative organism.

3.1.1.3 Fungal septic arthritis

Fungal organisms were only isolated in 1.7% (*n* = 2) of the patients. The causative organisms were *Cryptococcus neoformans* and *Aspergillus niger*.

3.1.2 Joint involvement

After the initial exclusion process, there were 184 patients remaining. Most of the affected joints were knees (64%), with elbows following at 15% (see Figure 3.4). Furthermore, there were some patients (*n* = 7) that had multiple joint involvement (see Table 3.2), i.e. they had surgery to more than one joint in the same sitting. The total number of individual joints drained tallies up to 203.

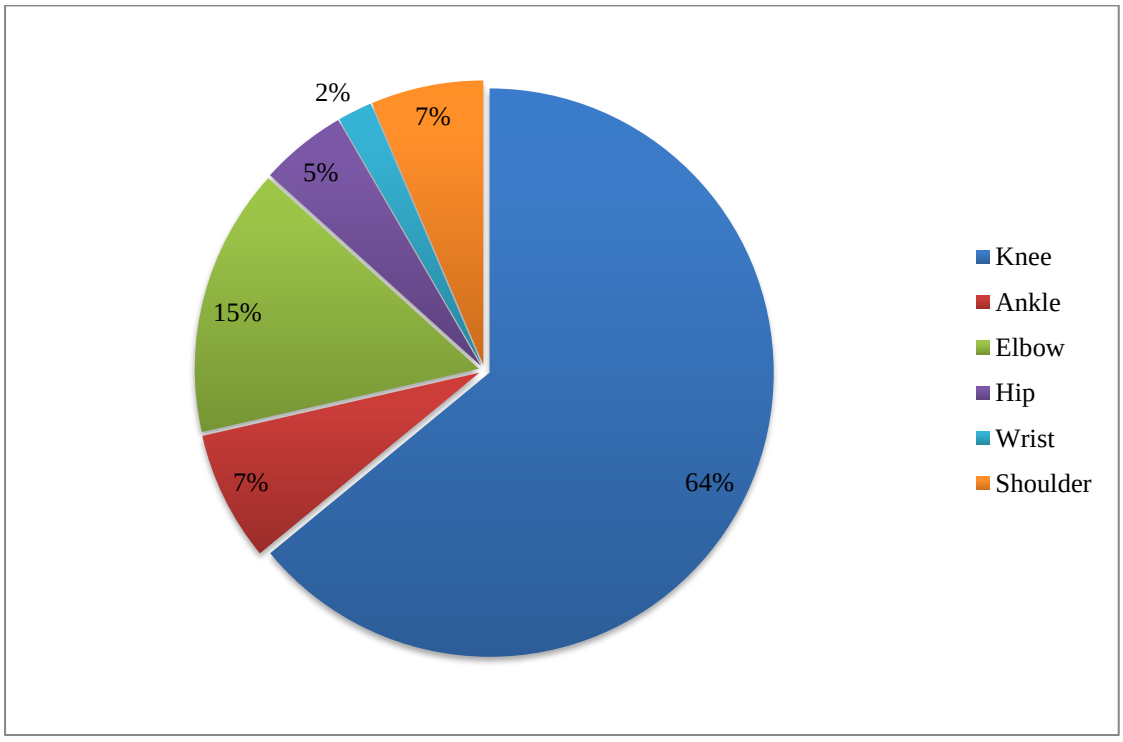


Figure 3.4 Pie chart displaying breakdown of all joints drained surgically during the study period

Table 3.2 Summary of poly-articular arthrotomies

Multiple Joints (N)	**Number (*n*)**	**Percentage**
Bilateral knees	2	1.0%
Knee + ankle	1	0.5%
Knee + shoulder	2	1.0%
Elbow + Shoulder	1	0.5%
Knee + bilateral ankles	1	0.5%
TOTAL	**7**	**3.4%**

3.1.2.1 Joint involvement in bacterial septic arthritis

In the cases of confirmed bacterial septic arthritis (*n* = 76), there were four patients with multiple joint involvement. Thus, the total count of joints was 82, as summarised in Figure 3.5.

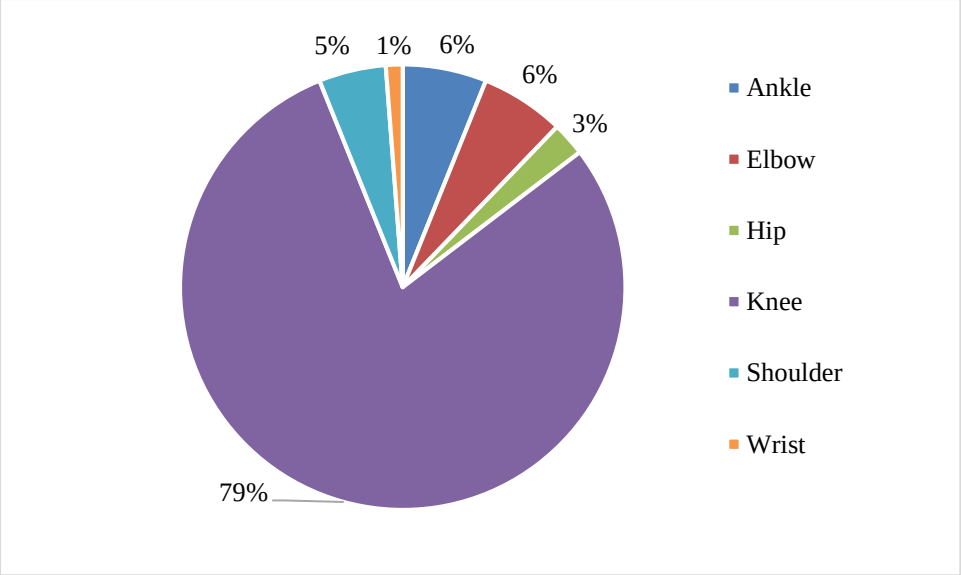


Figure 3.5 Pie chart summarising joint involvement in bacterial septic arthritis

Seventy-nine percent of cases of bacterial septic arthritis involved the knee joint (*n* = 65), followed by the ankle and elbow joints (6%, respectively) and the shoulder joint (5%). Bacterial infection of the hip and wrist joints in adults was uncommon.

3.1.2.2 Joint involvement in tuberculous arthritis

There were total of 11 cases of confirmed tuberculous arthritis. TB affected the lower limb more than the upper limb, with most cases involving the knee and hip joints (64% and 18%, respectively), and less so in the ankle and elbow joints. In this series, there was no confirmed tuberculous infection of the shoulder joint. See Figure below.

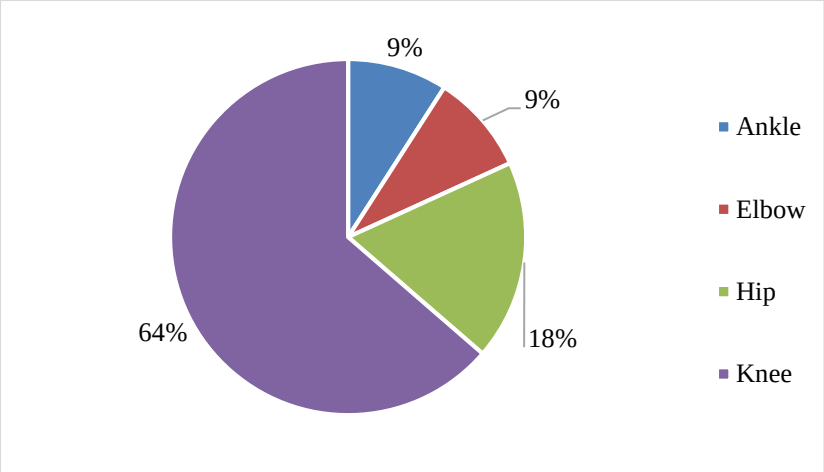


Figure 3.6 Pie chart summarising joint involvement in tuberculous arthritis

3.1.2.3 Joint involvement in fungal arthritis

Fungal arthritis was rare, with only two cases being diagnosed in this series. One patient had multiple joint involvement (knee and ankle), and the other patient had single joint involvement (knee). Therefore, the knee was involved in 66% of joints affected by fungal arthritis.

3.1.2.4 Joint involvement in negative arthrotomies

Once again, the knee joint predominated the number of arthrotomies (61%) (see Figure 3.7). There was a relatively similar distribution as in the bacterial septic arthritis group. There were also proportionately more hips in this group than in the bacterial group.

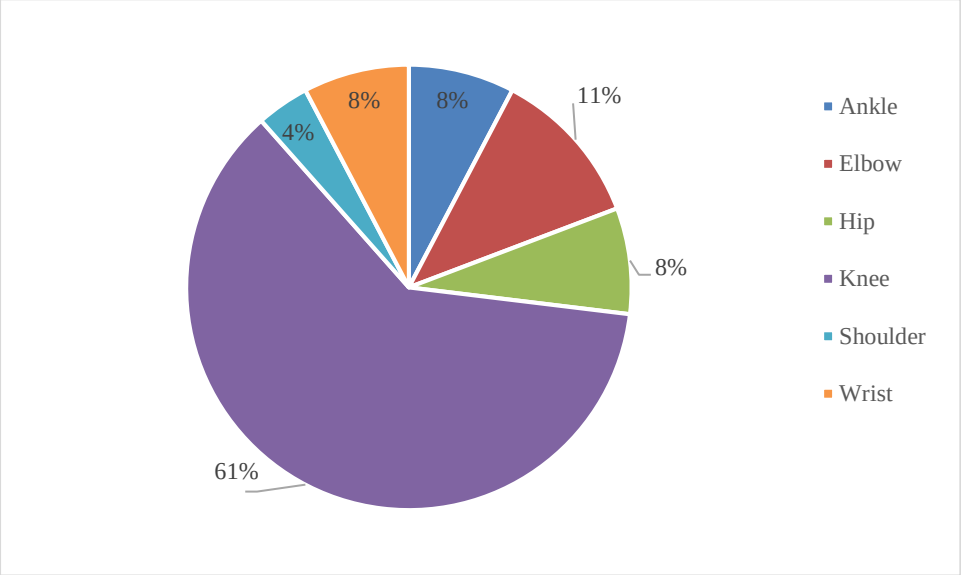


Figure 3.7 Pie chart summarising joint involvement in negative arthrotomies

3.1.3 Age and sex distribution

In all groups, there was an average male to female ratio of approximately 2:1. The individual pie charts are displayed in Figure 3.8. With only 2 patients in the fungal group, there was a 1:1 distribution of males to females.

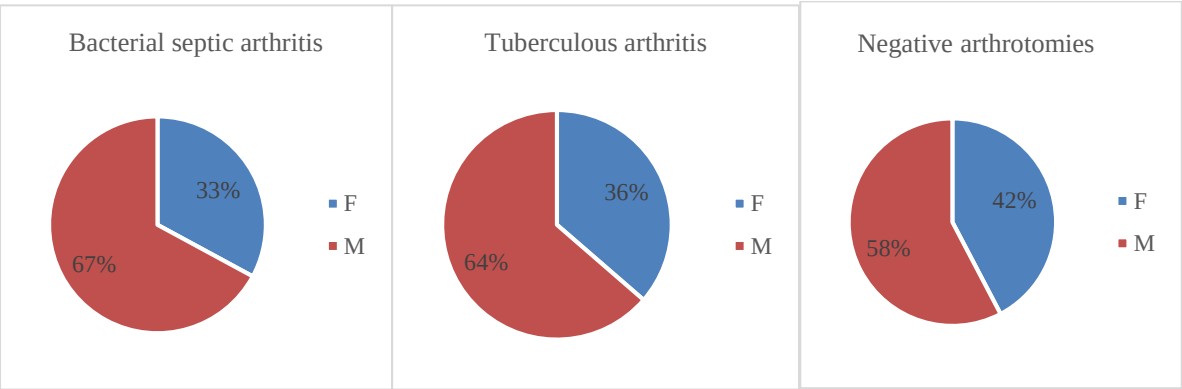


Figure 3.8 Pie charts displaying the sex distribution in the different groups (M = Male; F = Female)

The mean age of all the groups was 42 years (+/- 3 years). The age range was 18 years to 79 years, with 75% of patients being under the age of 50 years. Furthermore, within the different age groups, the male to female ratio was still approximately 2:1 (see Figure 3.9).

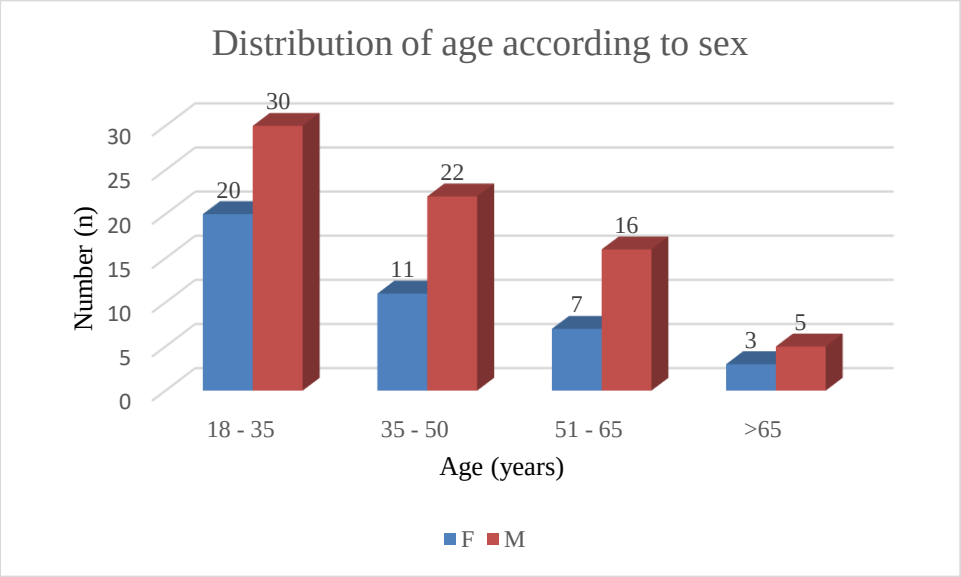
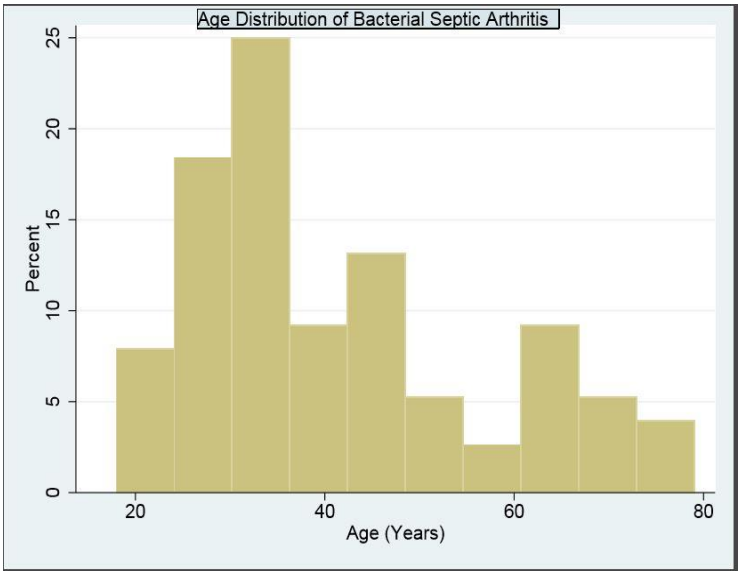


Figure 3.9 Chart displaying distribution of age according to sex (F = Female; M = Male)

With regards to the different groups, the following histograms display the salient points regarding the age distributions.



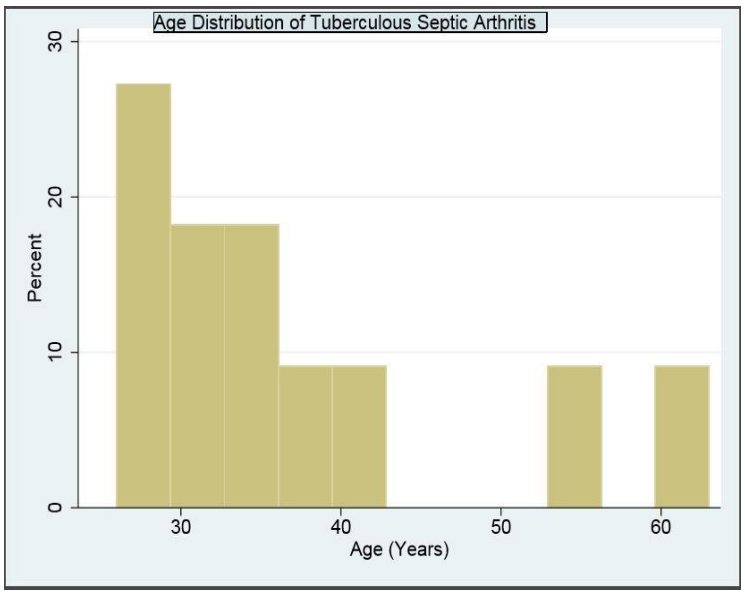
Bacterial septic arthritis

Mean age = 41 years (+/- 3years)

Range = 18 – 79 years

75% below age 50 years

Figure 3.10 Histogram displaying age distribution in bacterial septic arthritis

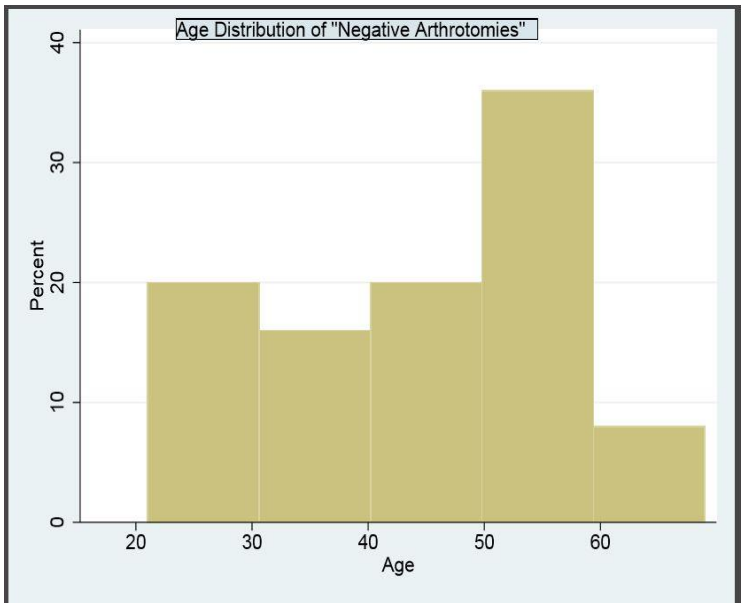


Tuberculous arthritis

Mean age = 37 years (+/- 10 years)

67% below age 40 years

Figure 3.11 Histogram displaying age distribution in tuberculous arthritis



Negative arthrotomies

Mean age = 43 years (+/- 3years)

55% below age of 50 years

Figure 3.12 Histogram displaying the age distribution in negative arthrotomies

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3.1.4 Time to surgery

Due to the urgent nature of bacterial septic arthritis, the time from initial diagnosis to surgery is of critical importance. The mean time from diagnosis to surgery in the bacterial group was 2.3 days (+/- 0.5 days). The shortest time to surgery was 0 days (i.e. a matter of hours), whilst the longest was 12 days (see Figure 3.13).

Within the negative arthrotomy group, the mean time to surgery was 2.1 days (+/- 0.8 days). The shortest time to surgery was 0 days, whilst the longest was 8 days.

Within the TB group, the mean time to surgery was 3.5 days (+/- 2.5 days). The shortest time to surgery was 1 day, whilst the longest was 12 days.

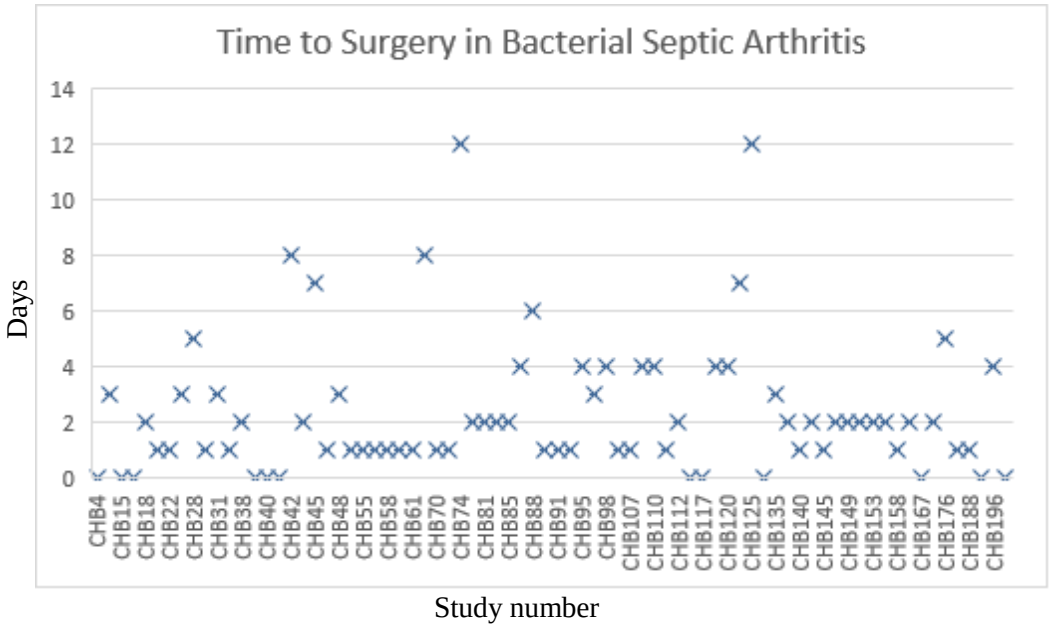

Figure 3.13 Scatterplot displaying the distribution of time to surgery

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3.1.5 Co-morbidities

The co-morbid conditions and other systemic illnesses included:

- HIV
- Gout
- Diabetes Mellitus
- Rheumatoid arthritis
- Others

3.1.5.1 HIV

In this study, 51% (*n* = 59) of the patients were HIV-positive throughout the entire group and 2% (*n* = 2) were confirmed HIV-negative. The remainder of the patients (47%) had unknown HIV statuses, i.e. they were either not offered HIV testing, or they declined to be tested.

Of the HIV-positive patients, 38% (*n* = 44) were previously known with HIV (having been diagnosed prior to admission) and 13% (*n* = 15) were newly diagnosed on the current hospital admission (see Figure 3.14).

Of those who were previously known with HIV, 66% (*n* = 29) were taking Anti-Retroviral Therapy (ART) while 34% (*n* = 15) were not. Since they were unaware of their diagnoses, those who were newly diagnosed HIV positive were not on ART (see Figure 3.14).

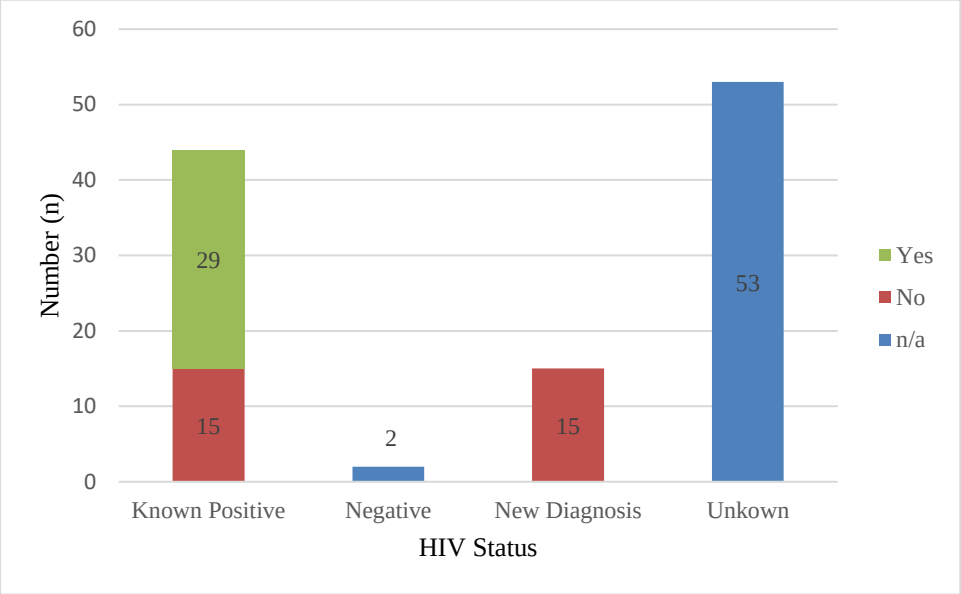

Figure 3.14 Bar graph displaying breakdown of HIV status of all patients (Yes = on ART; No = Not on ART; n/a = not applicable).

As depicted in Table 3.3, we can see that 51% (*n* = 40) of the patients with bacterial septic arthritis were HIV-positive (37% known, 14% new diagnosis). Sixty-six percent (*n* = 19) of those with a prior diagnosis of HIV were already taking ART.

Sixty-four percent (*n* = 7) of the patients with TB arthritis were HIV-positive. Once again, 66% of those with a prior diagnosis of HIV were already taking ART.

One hundred percent (n = 2) of the patients with fungal arthritis were HIV-positive, and both patients were known with HIV, and were already on ARV's.

Thirty-nine percent (n = 9) of the patients who had "negative arthrotomies" were HIV-positive (26% known, 13% new diagnosis). Sixty-six percent of those with a prior diagnosis of HIV were taking ARV's.

Table 3.3 Breakdown of HIV statuses of each group

HIV STATUS	GROUP				
	Bacterial	Fungal	Negative arthrotomies	TB	Total
Known Positive	**29**	**2**	**6**	**6**	**43**
Not on ARV's	10		2	2	14
On ARV's	19	2	4	4	29
Negative	**1**		**1**		**2**
New Diagnosis	**11**		**3**	**1**	**15**
Unknown	**37**		**13**	**4**	**54**
Grand Total	**78**	**2**	**23**	**11**	**114**

CD4 count levels were checked for most of the HIV-positive patients. Fourteen percent (n = 6) of those who had a known diagnosis of HIV (all of whom were on ARV's), did not get CD4 counts done. None of the HIV-positive patients had viral load levels checked.

The mean CD4 count of the patients who were taking ART was 474 cells/mm^3 (+/- 181), with the lowest CD4 being 20 cells/mm^3 and the highest being 1316 cells/mm^3. The mean CD4 count for the patients who were HIV-positive but not taking ART was 306 cells/mm^3 (+/- 136), with the lowest CD4 count being 40 cells/mm^3 and the highest being 779 cells/mm^3. The mean CD4 count of the patients who were newly diagnosed HIV-positive was 258 cells/mm^3 (+/- 105). The lowest CD4 in this group was 26 cells/mm^3 and the highest was 579 cells/mm^3. These findings are displayed in Figure 3.15.

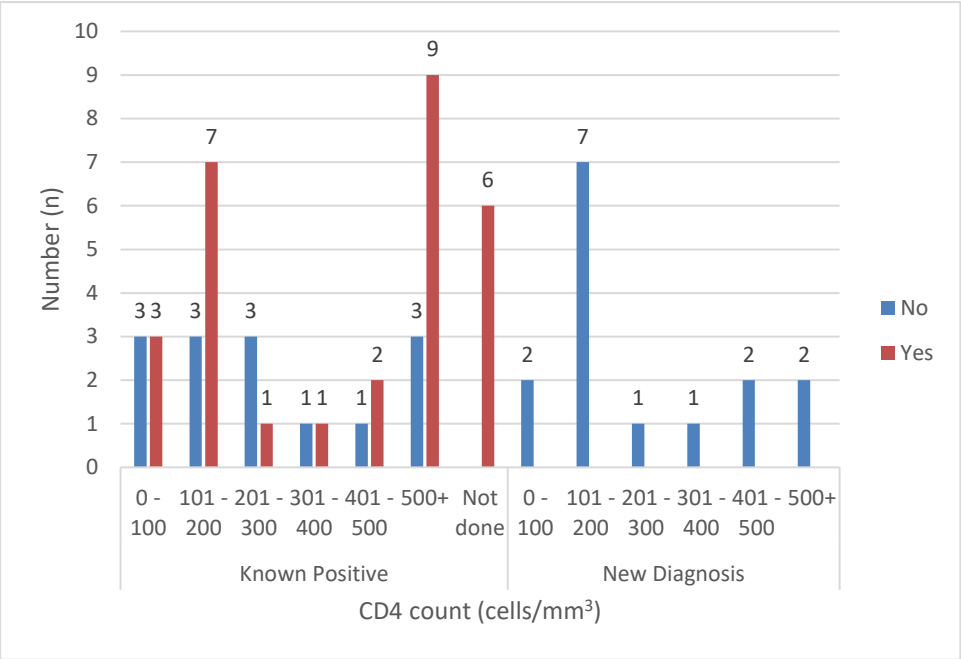

Figure 3.15 Bar graph displaying the range of CD4 counts in patients taking ART and not taking ART (Yes = On ART; No = Not on ART).

In the bacterial septic arthritis group, the mean CD4 count was 376 cells/mm^3 (+/- 112). More in-depth analysis within this group showed the mean CD4 of those who were on ART was higher (516 cells/mm^3) than the mean CD4 of those who were not on ART (278 cells/mm^3). This difference was found to be statistically significant (p = 0.03). Of note, 26% (n = 12) of the HIV-positive patients in the bacterial group had a CD4 count above 500 cells/mm^3.

In the TB group, the mean CD4 count was 155 cells/mm^3 (+/- 100). The patients on ART had a mean CD4 count of 185 cells/mm^3 (+/- 156). There were only three HIV-positive patients who were not on ART in this group, all of whom had CD4 counts below 200 cells/mm^3 (their average CD4 count was 126 cells/mm^3).

There was a statistically significant difference in the mean CD4 count of the bacterial group and TB group (p = 0.001). However, the difference in the mean CD4 count between the bacterial and negative arthrotomy groups was not statistically significant (p = 0.18).

There were only two patients in the fungal group. Both were HIV-positive and were taking ART. Both their CD4 counts were below 200 cells/mm^3.

In the negative arthrotomy group, the mean CD4 count of all the patients was 530 cells/mm^3 (+/-340).

With regards to causative bacterial organisms in HIV, there was no organism isolated in 47% (*n* = 18) of the cases. Of the cases where organisms were isolated, the most common causative bacterial organism was *S. aureus* (45% of the positive joint cultures). *S. pneumoniae* made up 25% of the positive joint cultures (see Table 3.4).

Table 3.4 Summary of bacterial organisms isolated in joint cultures of HIV-positive patients

Organism	**Frequency (*n*)**	**Percent (%)**
E. coli	3	15
S. agalactiae	1	5
S. aureus	9	45
S. pneumoniae	5	25
S. pyogenes	1	5
Salmonella species	1	5
Total	**20**	**100**

3.1.5.2 Gout

The serum uric acid (used as a diagnostic aid for gouty arthritis) was only checked in 25% (*n* = 28) of the entire group. High serum uric acid (above 0.41 mmol/L), was confirmed in 4% (*n* = 3) of the bacterial group and 12% (*n* = 3) of the negative arthrotomy group. These results have to be interpreted with caution, as a high uric acid is only suggestive of gout in the presence of other clinical criteria.

3.1.5.3 Diabetes Mellitus

Nine percent (*n* = 7) of the bacterial group were confirmed to be diabetic, all with uncontrolled sugar levels. The mean HBA1c for this group was 10.3% (+/- 2.6). There was only one confirmed diabetic in the negative arthrotomy and fungal groups, respectively.

3.1.5.4 Rheumatoid Arthritis

Rheumatoid arthritis was confirmed in 4% (*n* = 4) of the entire group. These patients were all referrals from the rheumatology department and were therefore, diagnosed by rheumatologists. Two percent were in the bacterial group and 1% were in the TB and negative arthrotomy groups, respectively.

3.1.5.5 Other

There was one haemophiliac in this study (study number CHB90). *S. aureus* was isolated both in blood and joint cultures (knee) for this patient.

There was one patient with chronic osteomyelitis of the femur (study number CHB149), who developed septic arthritis of the knee. *Serratia marcescens* was the organism isolated from the knee joint.

One patient was documented to have Systemic Lupus Erythematosus (study number CHB115). This patient had bacterial septic arthritis of the knee. No organisms were isolated from blood or joint.

One patient had chronic renal failure (study number CHB153). *S. pneumoniae* was isolated from the knee joint in this patient.

3.1.6 Septic markers

Blood testing for markers of infection were routinely taken in most of the patients. These blood tests were, namely: white cell count (WCC); serum C-Reactive Protein (CRP); and Erythrocyte Sedimentation Rate (ESR). With only two patients in the fungal group, further analysis of the septic markers was not done.

3.1.6.1 WCC

The mean WCC in the bacterial group was 12.31 x 10^9/L (+/- 1.48). This is higher than the normal reference range of 4 – 10 x10^9/L. The lowest level was 4.06 x 10^9/L and the highest was 32.75 x 10^9/L (see Figure 3.16).

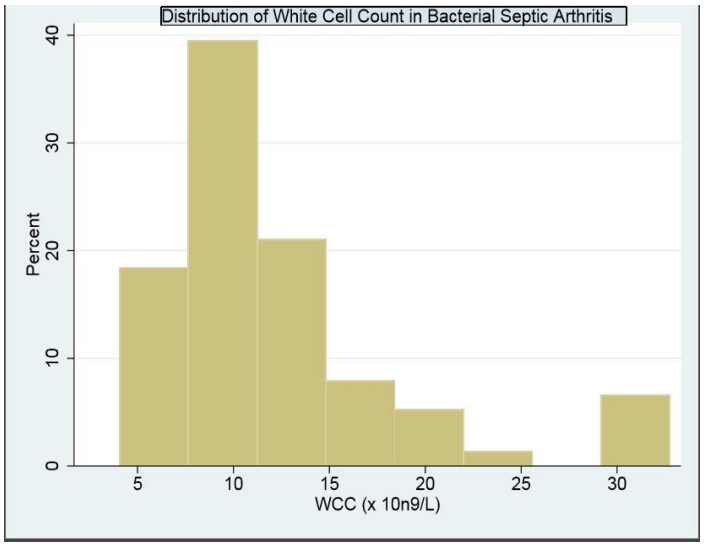

Figure 3.16 Histogram displaying the distribution of WCC in bacterial septic arthritis

The mean WCC in the TB group was 6.71 x10^9/L (CI = 1.96). This is within the normal reference range. The highest level was 12.13 x10^9/L and the lowest was 2.17 x10^9/L (see Figure 3.17).

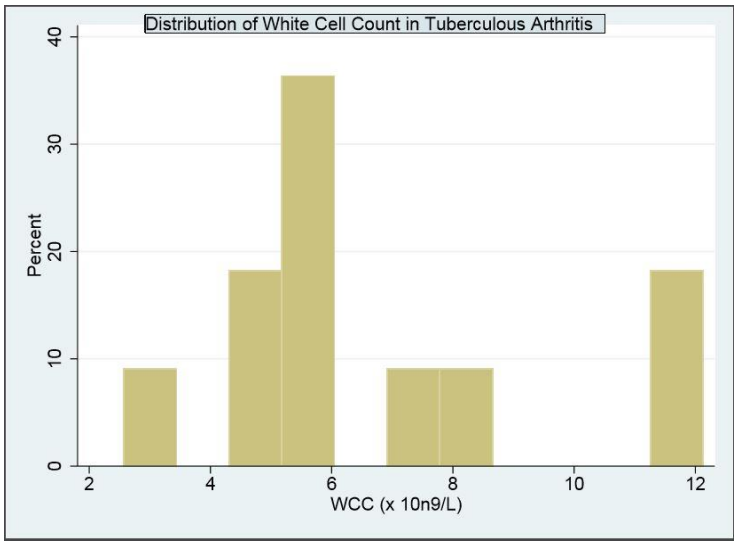

Figure 3.17 Histogram displaying the distribution of WCC in TB arthritis

The mean WCC in the negative arthrotomy group was 9.27 x 10^9/L (+/- 1.69). This is within the normal reference range. The highest level was 20.07 x 10^9/L and the lowest was 4.23 x 10^9/L (see Figure 3.18).

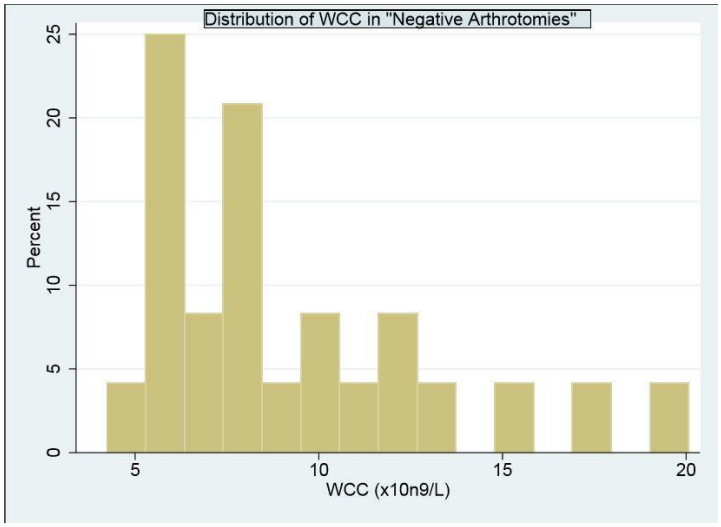

Figure 3.18 Histogram displaying the distribution of WCC in negative arthrotomies

3.1.6.2 CRP

The mean CRP in the bacterial group was 219 mg/L (+/- 30), which is higher than the reference range of 0 – 10 mg/L. The highest level was 584 mg/L and the lowest was 42 mg/L (see Figure 3.19).

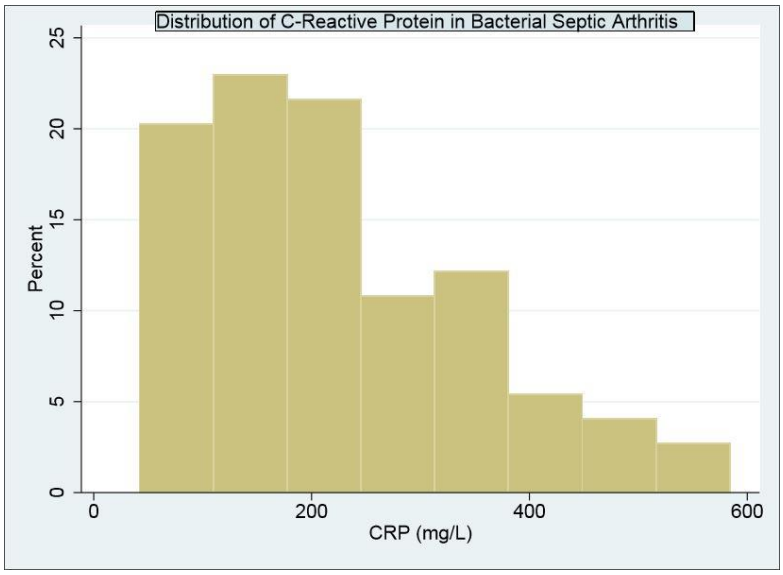

Figure 3.19 Histogram displaying the distribution of CRP in bacterial septic arthritis

The mean CRP in the TB group was 75mg/L (+/- 26). This is higher than the normal reference range. The highest level was 169 mg/L and the lowest was 22 mg/L (see Figure 3.20).

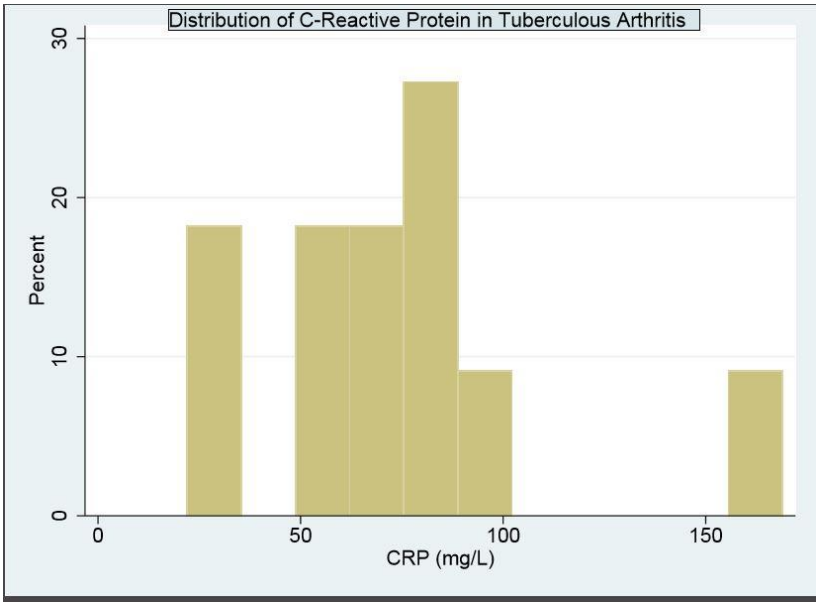

Figure 3.20 Histogram displaying the distribution of CRP in TB arthritis

The mean CRP in the negative arthrotomy group was 73 mg/L (+/- 22). This is also higher than the normal reference range. The highest level was 183 mg/L and the lowest was 1 mg/L (see Figure 3.21).

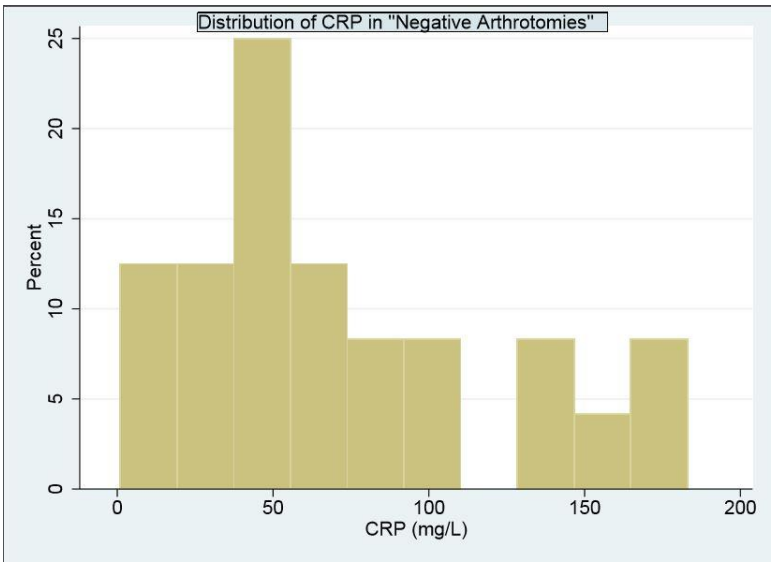

Figure 3.21 Histogram displaying the distribution of CRP in negative arthrotomies

3.1.6.3 ESR

The mean ESR in the bacterial group was 84 mm/hr (+/- 11). This is higher than the normal reference range of 0 – 10 mm/hr, but lower than 100 mm/hr. The highest level was 150 mm/hr and the lowest was 1 mm/hr (see Figure 3.22).

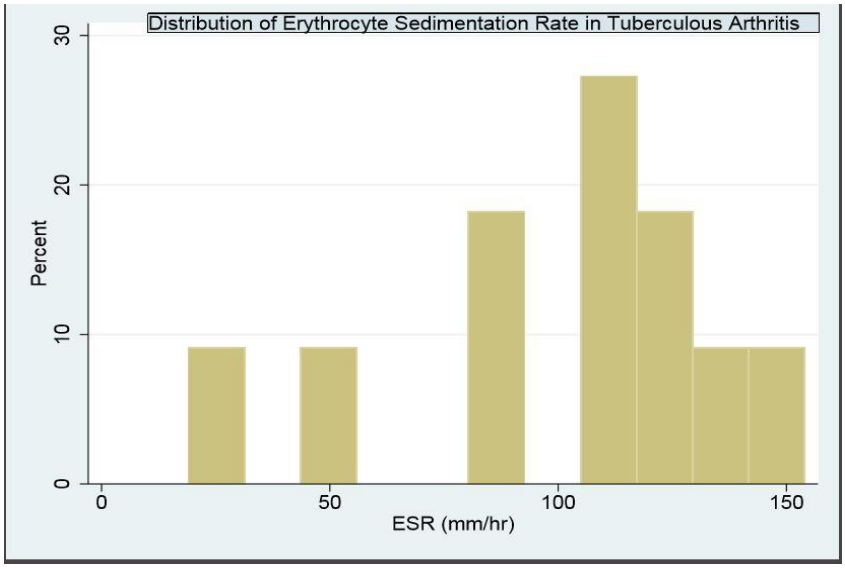

Figure 3.22 Histogram displaying the distribution of ESR in bacterial septic arthritis

The mean ESR in the TB group was 102 mm/hr (+/- 25). This is higher than the normal reference range, and above 100 mm/hr. The highest level was 154 mm/hr and the lowest was 19 mm/hr (see Figure 3.23).

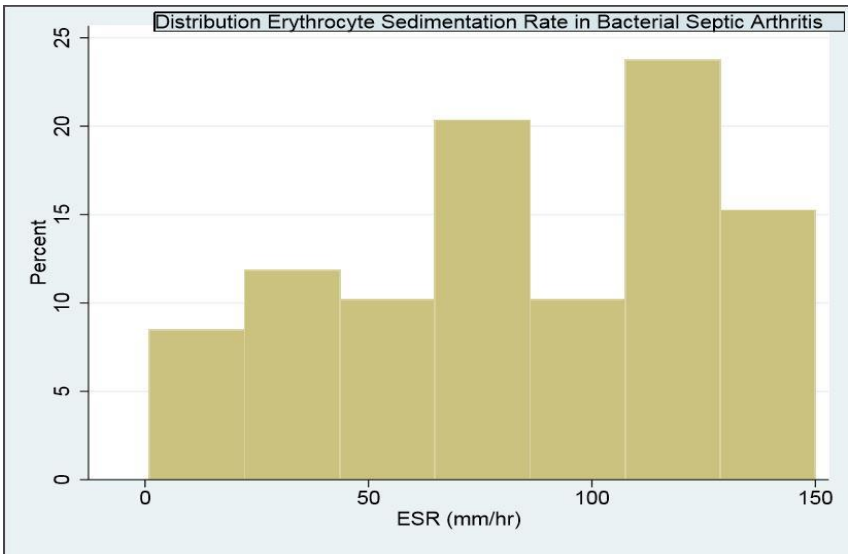

Figure 3.23 Histogram displaying the distribution of ESR in TB arthritis

The mean ESR in the negative arthrotomy group was 58 mm/hr (+/- 17). This is also higher than the reference range but lower than 60 mm/hr. The highest level was 133 mm/hr and the lowest was 1 mm/hr (see Figure 3.24).

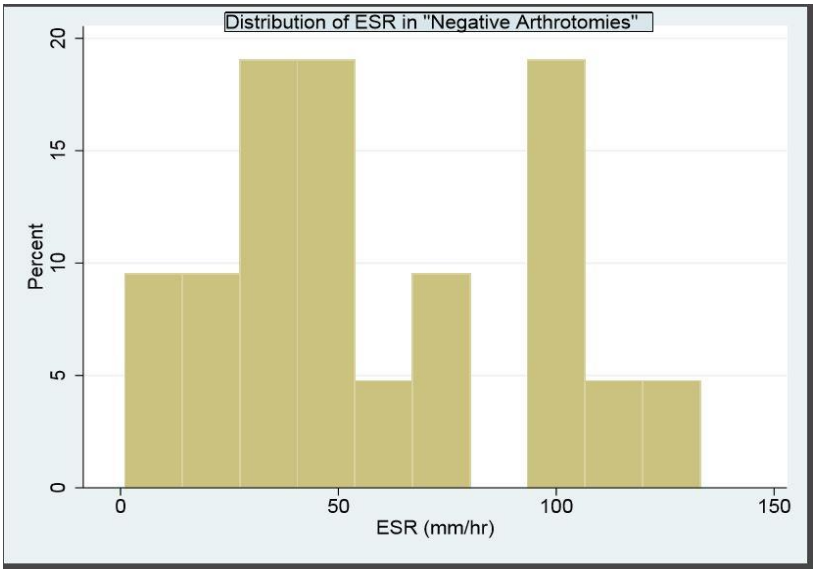

Figure 3.24 Histogram displaying the distribution of ESR in negative arthrotomies

3.6.1.4 Analysis between groups

As depicted in Table 3.5, ANOVA testing of the septic markers between the groups showed that differences in the WCC and the ESR were statistically significant, whereas the differences in the CRP were not statistically significant.

Table 3.5 ANOVA testing of septic markers between groups

Mean results	**Bacterial**	**TB**	**Negative Arthrotomies**	***p*-value**
WCC (x 10^9/L)	12.31	6.71	9.27	0.00314
CRP (mg/L)	219	75	73	2.79
ESR (mm/hr)	84	102	58	0.00791

3.6.1.5 Septic markers in HIV

In bacterial septic arthritis, the mean WCC was lower in HIV than in the whole group (11.24 +/- 1.94). The mean CRP was also lower (205 +/- 40). The mean ESR was slightly higher than in the whole group (96 +/- 13). There were not enough confirmed HIV negative patients to make a comparison between HIV-negative and HIV-positive groups.

Analysis within the HIV-positive group revealed that between those who were on ART and those who were not, the differences in septic markers were not statistically significant (see Table 3.6).

Table 3.6 Analysis of septic markers of HIV-positive patients in bacterial septic arthritis

Mean results	**On ART**	**Not on ART**	***p*-value**
WCC ($x 10^9$/L)	10.52	11.88	0.24
CRP (mg/L)	228	185	0.13
ESR (mm/hr)	105	88	0.10

In TB arthritis the mean WCC was also lower than in the whole group (7.52 +/- 3.2). In HIV-positive and HIV-negative individuals, the WCC was within the normal reference range. The patients on ART tended to have higher WCC than those who were not, though this difference was not statistically significant.

The mean CRP was higher in HIV than in the whole group (90 +/- 34). The mean CRP tended to be lower in those patients who were on ART versus those who were not, though this difference was not statistically significant (see Table 3.8).

The mean ESR was 100 mm/hour (+/- 39), which is close to the value for the whole TB group (102 mm/hour). There was also no difference between the patients on ART those who were not on ART (Mean ESR = 97 mm/hr) (see Table 3.8).

Table 3.8 Analysis of septic markers of HIV-positive patients in tuberculous arthritis

Mean results	**On ART**	**Not on ART**	***p*-value**
WCC (x 10^9/L)	5.97	8.63	0.31
CRP (mg/L)	81	121	0.29
ESR (mm/hr)	97	97	0.50

It is, however, difficult to make reliable statistical inferences because the same size is small in the TB group (n = 11).

CHAPTER 4

4 Discussion

This study endeavoured to clarify what the landscape of septic arthritis is like in a tertiary hospital setting such as CHBAH and compare it to data from elsewhere in Africa and the rest of the world. Over a four-year period, we took 198 patients to theatre for suspected articular sepsis. Due to incomplete clinical records and laboratory results, unfortunately we could only analyse 63% (*n* = 114) of the data. We treated 76 cases of bacterial septic arthritis during this period. There were also 11 cases of tuberculous arthritis and two cases of fungal arthritis. The rest (*n* = 25) were negative arthrotomies.

The mean age of patients with bacterial septic arthritis in our study was 41 years (+/- 3years). This is significantly lower than the age reported in other studies from more developed countries. Comparatively, Clerc *et al*. found a mean age of 57 years in their study[10] and Gupta *et al*. found a median age of 63 years in theirs[9]. In developing countries, such as the study coming out of West Africa, the mean age in their small sample was 35 years for the 17 – 60 age group, and 68 years for the > 60 age group[1]. Our study compares favourably with our South African counterparts, as Matekane *et al*. found a mean age of 44 in their study[6], and Nel *et al*. found that most of their patients were under 50 years old[7]. The reasoning behind this is multi-factorial. Firstly, low socio-economic status has been found to be a risk factor for septic arthritis[2,33]. According to Statistics South Africa, 56.8% of South Africans are living in poverty (most of them being under the age of 50)[34]. It stands to reason that most of our cases of adult septic arthritis will occur in patients younger than 50 years. Secondly, this could also be due to the fact that over 50% of our patients with septic arthritis were HIV-positive. According to UNAIDS, most of the persons living with HIV are in the younger age group[22]. This could also account for the lower mean age in the TB group (37 years +/- 10), most of whom were HIV-positive.

In accordance with the literature, this study found that males were affected more than females (male to female ratio = 2:1). The actual ratio varies slightly to the numbers reported in Pretoria (1.3:1)[7], West Africa (1.5:1)[1], Glasgow (3:1 in rheumatoid arthritis, 1:1 in non-rheumatoid arthritis)[9], and New York (2.3:1)[4]. Our study also found that the ratio was consistent throughout the age groups.

Also in accordance with the literature, the knee was the most affected joint in bacterial (79%), tuberculous (67%) and fungal (66%) arthritis. In our study, knee involvement in bacterial septic arthritis was higher than that quoted in other studies (knee involvement 40% - 73%)[1,5,7,9,10]. This is likely due to the predilection of bacterial organisms, especially *S. aureus,* to infect the knee joint[33]. The ankle, shoulder and elbow were the next most commonly affected joints. Bacterial septic arthritis of the hip was rare in our study (1%). In contrast, TB arthritis of the hip was relatively high (18% of joints). Of note 3.4% of patients had poly-articular infections. This may have implications with regards to the level of the septic markers and outcomes (increased morbidity and mortality)[33]. Of note was the low rate of upper limb involvement in TB arthritis (9%) in this study, as compared with a study conducted in Thailand, which found 43% upper limb involvement[19].

In bacterial septic arthritis, we found that 55% of the joints yielded a positive culture. The majority of the organisms that were isolated were Gram-positives, with *S. aureus* and *S. pneumoniae* being the most common (42% and 21%, respectively). The most common Gram-negative organism was *E. coli*. This is somewhat different to the findings reported by Matekane *et al.*, who had a higher proportion of Gram-negative organisms (45%)[6]. The proportion of *S. aureus* in our study is different to that in other centres (58.6% in France[5], 25% in Pretoria[7]). This is likely due to the different microbiomes and resultant antibiotic stewardship in different hospitals. It is also likely the prevalence of different co-morbid illnesses in respective centres is not the same. We found a relatively high prevalence of *S. pneumoniae* in our series (21%). Interestingly, 56% of the patients who had *S. pneumoniae* were HIV-positive. The rest were not tested for HIV. It would be interesting to see if there is an association between HIV status and *S. pneumoniae*-osteoarticular sepsis in adults. In the paediatric HIV-positive population, *S. pneumoniae* has been isolated in up to 66.7% of

osteoarticular sepsis, as opposed to 9.7% in HIV-negative individuals[35]. The study by Ross *et al*. found the HIV prevalence in *S. pneumoniae* cases to be only 8%[15].

What was lacking in our study was a break-down of the drug-sensitivities of the organisms which were isolated. This was, however, extensively covered in the study by Matekane *et al*.[6].

The cases of TB arthritis in our series were mostly diagnosed by positive joint culture (45%). There has been an emergence of more cases being diagnosed by NAAT. In our series, 19% of the TB arthritis cases were diagnosed by these means. Nurwidyu *et al*. noted that one such NAAT, the XPert MTB/RIF Assay, allows for the rapid diagnosis of TB (within two hours)[36]. There is also the added benefit of ascertaining the sensitivity of the mycobacterium to one of the first-line anti-tuberculous drugs, Rifampicin. This suggests that we should be subjecting more, if not all, of the cases of suspected TB arthritis to a NAAT.

The most prevalent co-morbidity in this study was HIV. Fifty-one percent of the bacterial group, 64% of the TB group and 100% of the fungal group were HIV-positive. This is significantly higher than the numbers quoted from developed areas like New York (13%)[4]. In Pretoria they had an HIV seroprevalence of 13% as well, albeit they had offered HIV testing to less than 25% of their patients[7]. Unfortunately, quite a high proportion of all our patients (47%) had unknown HIV statuses. The mean CD4 count of HIV-positive patients in the bacterial group was higher than 350 cells/mm^3, whereas that of the TB group was lower than 200 cells/mm^3. This difference was statistically significant ($p = 0.001$) and would seem to suggest that patients with lower CD4 counts are prone to TB, whereas those with relatively higher CD4 counts get bacterial infections. It also appears that CD4 counts which are deemed to be "normal" (i.e. the patient's immune status has been reconstituted) are not protective when it comes to susceptibility to serious bacterial infections. This is evidenced by the relatively high proportion of patients in the bacterial group who had CD4 counts above 500 cells/mm^3 in our study (26%). As noted earlier, it would seem that *S. pneumoniae* has a predilection for the HIV-positive population. However, a formal study with a bigger sample size would need to be done to elucidate this.

Of the other co-morbid conditions, we found that 4% of the patients with bacterial septic arthritis possibly had concurrent acute gout. Twelve percent of the negative arthrotomies

were attributable to an acute gout attack, and as such the patients were subjected to unnecessary surgery. The prevalence of diabetes in the bacterial group was 9%, and all these patients had poor glycaemic control (mean HBA1c = 10.3 +/- 2), thus corroborating the findings by Hine *et al*. that poor glycaemic control predisposes to bacterial infections[9]. Rheumatoid arthritis was rare in our series (4%) but this is likely due to underreporting as a result of poor record-keeping in the clinical records. Considering that rheumatoid arthritis is a risk factor for septic arthritis, as well as the fact that these patients periodically take immune-suppressing medication, one would expect the prevalence of rheumatoid arthritis in septic arthritis to be higher than the number stated above. A prospective cohort study is needed to investigate the actual prevalence.

With regards to septic markers it is difficult in adult patients to determine if the cause of the inflamed joint is due to infective or non-infective causes. Our study found that the mean WCC in bacterial septic arthritis (12.31 x 10^9/L) was higher than the normal reference range, whereas the WCC in TB and negative arthrotomies (6.71 x 10^9/L and 9.27 x 10^9/L, respectively) were within the normal reference range. The differences among the three groups was statistically significant (p = 0.003). The mean ESR in bacterial septic arthritis (84 mm/hour) was eight-times higher than the normal reference range, and the mean ESR in TB (102 mm/hour) was ten-times higher than the normal reference range. The mean ESR in the negative arthrotomy group (58 mm/hour) tended more towards 60. The differences in ESR among these groups was statistically significant (p = 0.008). Therefore, it suggests that an ESR above 100 mm/hour is likely to be due to TB, an ESR of 60 to 100 mm/hour is likely due to bacterial septic arthritis, and below 60 mm/hour is likely due to other causes (e.g. gout). The mean CRP in the bacterial group (219 mg/L) was twenty-times higher than the normal reference range, whereas the CRP in TB and negative arthrotomies was relatively the same (75 mg/L and 73 mg/L, respectively). The differences in CRP among the three groups was not statistically significant (p = 2.79), probably due to similar variances between the TB and negative arthrotomy groups. What we can read from these results is that bacterial septic arthritis tends to have very high CRP levels (more than ten-times the normal value), whereas CRP levels below 100 mg/L are less likely to be of bacterial aetiology. This is where the ESR level is very important to distinguish between infective and non-infective causes. In the study by Courdec *et al*. they found that a WCC greater than 10,000 cells/L was 50% sensitive and 61% specific for bacterial septic arthritis[5]. Furthermore, they found that an ESR above

15mm/hour was 94% sensitive and 23% specific, while a CRP above 15mg/L was 92% sensitive and 18% specific. Interestingly, a CRP above 100 mg/L (a prominent feature in our study) was found to be 58% sensitive and 66% specific. The findings suggest that CRP level is better at ruling out a septic arthritis rather than helping to diagnose it. Perhaps what ought to be looked into in the South African setting is the value of the procalcitonin (PCT) level in the diagnosis of bacterial septic arthritis. A high PCT level (above 0.5ng/mL) is highly suggestive of bacterial infection. Paosong *et al*. evaluated the use of PCT in bacterial septic arthritis and made the following findings:[37]

Table 3.8 Diagnostic accuracy of PCT level in bacterial septic arthritis

PCT level (ng/mL)	**Sensitivity**	**Specificity**	**PPV**	**NPV**
> 0.5	59%	84%	66.7%	79.2%
> 0.66	69%	86%	69.6%	79.6%

The overriding sentiment in the literature is that we ought to be utilising the jWBC more to aid in diagnosis of septic arthritis. However, the clinician should utilise both clinical examination and laboratory results to reach a diagnosis.

The septic markers in the HIV-positive patients in our study were slightly different to the group as a whole. HIV-positive patients tended to have a lower WCC in bacterial arthritis (11.24 x 10^9/L *vs* 12.31 x 10^9/L), and slightly higher WCC in the TB group (7.52 x10^9/L *vs* 6.71 x 10^9/L). CRP levels of HIV-positive patients were also slightly lower in the bacterial group (205 mg/L *vs* 219 mg/L), whereas in TB they were slightly higher (90 mg/L *vs* 75 mg/L). The ESR in HIV-positive patients was essentially the same, or higher, compared to the group as a whole (both in bacterial and TB arthritis). This corroborates the findings by Jellis, who noted that in TB, HIV-positive patients tend to have high (if not higher) ESR's compared to those of HIV-negative patients[38]. Our study did not have a big enough HIV-negative group to make meaningful comparisons. Furthermore, we found that there was no statistically significant difference in septic markers between the patients on ART *versus* those who were not on ART.

The main limitation of our study was the retrospective nature of the study design. This resulted in a relatively low sample size. Furthermore, trying to collect retrospective data of patients' hospital records proved to be difficult, as there was a lot of missing data. Therefore, the true prevalence of co-morbid conditions may be different to the numbers reported in this study. This may also affect the quality of the statistical analyses which were done for parameters such as septic markers. Another issue is the patients who were culture-negative in the bacterial and TB groups. A diagnosis relied on methods which are not the so-called gold standard (positive joint culture). As such there may have been false positives, which would affect the diagnostic accuracy of the septic markers. Converse to that, is the possibility of there being false negatives in the negative arthrotomy groups, which would also affect the diagnostic accuracy of the septic markers. The use of Newman's criteria hopefully mitigated the false positive and false negative rates.

4.1 Recommendations

Based on the results obtained from this study the following recommendations are made:

- In future, the study should be a prospective study design, so that a cohort of patients can be followed up. In that way, we can get a true sense of the burden of HIV (and other co-morbidities) in osteoarticular sepsis. Also, meaningful inferences can be made by comparing HIV-positive and HIV-negative cohorts. A prospective study will also ensure that data are collected reliably and consistently. This will greatly improve the quality of the statistical analysis.
- We recommend routine HIV testing, serum uric acid level, as well as a serum HBA1c in patients being worked up for osteoarticular sepsis. We also recommend routine polarised light microscopy and crystal analysis of joint fluid.
- As part of the diagnostic work-up for osteo-articular sepsis, we recommend that a serum PCT as well as jWBC be routinely done by the clinicians in the emergency and orthopaedic departments. This will greatly reduce the false positive and false negative rates.
- Once a diagnosis of bacterial septic arthritis is made, the patient should be taken for urgent surgical debridement/arthrotomy (within eight hours). In our study, the mean

waiting time for theatre in the bacterial group was 2.3 days. The hospital system needs to be optimised to allow the orthopaedic surgeon to perform the surgery expediently.

- In cases of suspected tuberculous arthritis, the surgeon doing the arthrotomy must (in addition to the routine tests) send a tissue sample for GeneXpert testing. This would help diagnose those cases of TB that would not necessarily yield a positive culture.
- In terms of future directions, cytokine analysis of synovial fluid needs to be looked into. A bedside-rapid test must be designed, that will have a high sensitivity and specificity for joint infection however, this is expensive.

CHAPTER 5

5 Conclusion

Osteoarticular infection remains a big problem in our setting of a developing country, where 56% of people are living in poverty. In our tertiary institution, we operated on more than 200 patients in four years, for suspected articular sepsis. Over 75% of these cases were due to bacterial infection and tuberculosis combined. Fungal arthritis was rare in our study.

Gram-positive organisms predominate as the causative organisms in bacterial septic arthritis, with *S. aureus* being the most commonly isolated. The prevalence of *S. pneumoniae* was relatively high in our series, with most of the cases having concurrent HIV infection. *MTB* and fungal infections are important considerations in the immunocompromised patient. There is also emerging reliance on NAAT in the diagnosis of mycobacterial infection.

The knee joint is the most commonly involved joint affected by infective processes. Our series had relatively few poly-articular infections.

Our series had a high HIV seroprevalence (51%), which is significantly higher than the numbers quoted in other studies. Uncontrolled diabetes mellitus was also a significant co-morbidity in our series.

Laboratory diagnosis remains a challenge, especially in the adult patient. It appears that 5-to 10-fold increases in CRP and ESR have a higher positive predictive value for infection, as opposed to inflammatory arthropathies. More work needs to be done, especially in the HIV-positive population, to elucidate the challenges that the clinician faces in the diagnosis of osteoarticular infection in adults.

6 References

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7 Appendices

Appendix A: Data Collection Sheet

Septic Arthritis in Adult Patients at Chris Hani Baragwanath Academic Hospital: A clinical Audit

Date of Surgery:

Study number:

Age:

Sex:

Side (left or right):

Co-morbidities:

- *HIV (Known; New Diagnosis; Negative; Not Tested):*
- *Diabetes:*
- *Rheumatoid:*
- *Other:*

Results:

- *WCC:*
- *CRP:*
- *Blood culture:*
- *Joint culture:*
- *ESR:*
- *HBA1c:*
- *CD4:*
- *VL:*

Appendix B: CHBAH Hospital CEO approval to conduct research

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 30 Oct 2017

TITLE OF PROJECT: Septic arthritis in adults at Chris Hani Baragwanath Academic Hospital: A clinical audit

UNIVERSITY:

Principal Investigator: LA Nhlapo

Department: Ortopaedics

Supervisor (If relevant): T Sefeane

Permission Head Department (where research conducted): Yes

Date of start of proposed study: Nov 2017
Date of completion of data collection: Dec 2019

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 30 October 2017

.....
Approved/Not Approved
Hospital Management
Date: 31/10/17

Received by: L Nhlapo
Date: 1/11/2017

Appendix C: Ethics Clearance Certificate

R14/49 Dr L Nhlapo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M171164

NAME: (Principal Investigator)	Dr L Nhlapo
DEPARTMENT:	School of Clinical Medicine Department of Orthopaedic Surgery Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Septic arthritis in adult patients at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	24/11/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr T Sefeane
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/12/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

01/03/2018
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES