Micro-Organisms causing Septic Arthritis in adult patients at Chris Hani Baragwanath Academic Hospital

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Declaration

I, Katleho Motseki Matekane, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university

_____ 12 July 2017

Signed: K.M. Matekane Date

Dedication

This work is dedicated to my beloved wife MmaKgotso and our daughters Leruo, Omphemele and Boitsebo whose understanding and whose sacrifice made it possible for me to do my work.

Thank you.

Abstract

Septic arthritis is a very common orthopaedic emergency. Surgical debridement and empiric antibiotic cover together make up the vital initial management of septic arthritis. Empiric antibiotic cover is determined using the most prevalent bacteria in a specific clinical setting given the patient profile. The purpose of the study was to determine the microbiological spectrum that is responsible for septic arthritis at our centre and the antibiotic sensitivity thereof. This retrospective study included 82 patients who were admitted with a diagnosis of septic arthritis. The microbiological and biochemical results of these patients were retrospectively reviewed. All patients older than 18 years with a clinical diagnosis of septic arthritis who were taken to theatre for an arthrotomy were included in the study. Gram positive species were more common compared to gram negative species at 51% and 40% respectively, with *Staphylococcus aureus* being the most common gram positive and *Pseudomonas species* the most common gram-negative pathogen. Antibiotic resistant bacteria like *Methicillin-resistant Staphylococcus aureus* and *Acinetobacter baumannii* were each found to be responsible in 7% of cases. The use of Cloxacillin as empiric antibiotic cover was effective in only 30% of cases. To increase cover the use of vancomycin as empiric antibiotic should be considered, as vancomycin had better empiric cover at 54% against all isolates. In cases of suspected *Streptococcal* infections, Penicillin or Erythromycin should be considered. Gram negative species are rarely isolated as offending organisms in septic arthritis, when found these infections can be difficult to treat. According to our study Amikacin and Gentamycin should be considered in all cases of suspected gram negative septic arthritis. Mycobacterium tuberculosis complex should be considered in patients at risk as the antibiotic treatment used is unique and for a relatively extended period compared to other bacteria. Regular microbiological profiling of bacteria in each centre is important in determining the appropriate empiric antibiotic treatment for septic arthritis.

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List of abbreviations

Abbreviations	Full term
A. Baumannii	*Acinetobacter baumannii*
C. Koseri	*Citrobacter koseri*
CNSA	*Coagulase negative staphylococcus*
CRP	C Reactive Protein
E. Aerogenes	*Enterobacter aerogenes*
E. Cloacae	*Enterobacter cloacae*
E. Coli	*Escherichia coli*
E. Faecalis	*Enterococcus faecalis*
E. Faecium	*Enterococcus faecium*
E. Species	*Enterobacter species*
ESR	Erythrocyte Sedimentation Rate
Group B Strep	*Streptococcus group B*
H. Parainfluenzae	*Haemophilus parainfluenzae*
K. Oxytoca	*Klebsiella oxytoca*
K. Pneumoniae	*Klebsiella pneumoniae*
K. Species	*Klebsiella species*
MRI	Magnetic resonance imaging
MRSA	*Methicillin-Resistant Staphylococcus aureus*
MTB	*Mycobacterium tuberculosis complex*
P. Aeruginosa	*Pseudomonas aeruginosa*
P. Mirabilis	*Proteus mirabilis*
S. Agalactiae	*Streptococcus agalactiae*
S. Anginosus	*Streptococcus anginosus*
S. Aureus	*Staphylococcus aureus*
S. Epidermidis	*Staphylococcus epidermidis*
S. Haemolyticus	*Staphylococcus haemolyticus*
S. Marcescens	*Serratia marcescens*
S. Pneumoniae	*Streptococcus pneumoniae*
S. Pyogenes	*Streptococcus pyogenes*
Streptococcus spp	*Streptococcus species*
V. Streptococcus	*Viridans streptococcus*
WCC	White Cell Count

Chapter 1 - Introduction and Literature Review

Septic arthritis is a term commonly used to describe acute joint infection caused by bacterial micro-organism, even though other micro-organisms like fungi, viruses and parasites can also cause septic arthritis (1). Presence of micro-organisms in the joint commonly presents as an acute mono-arthritis. These microbial joint infections usually respond well to early, adequate and appropriate treatment. This consists of an initial surgical drainage and debridement and empiric intravenous antibiotics. Inadequate treatment results in joint destruction from the inflammatory process and the microbiological cause. The consequence of which can be lifelong disability, and in the case of severe septicaemia, even death. This usually occurs in patients with underlying comorbidities, rheumatoid arthritis and the elderly (2).

The presence of a hot, swollen painful joint usually raises the suspicion of a septic arthritis. These clinical signs and symptoms however have long lists of differential diagnosis, in one study Non-gonococcal arthritis had a prevalence of only 27% amongst patients who presented to a casualty with such symptoms. Other conditions that should be considered as differential diagnosis are included in Table 1.1 below (3, 4). Incidence of septic arthritis in the general population is estimated at 2 − 10 per 100 000 patient years. Patients at high risk of developing septic arthritis (e.g. rheumatoid arthritis patients) have incidence as high as 70 cases per 100 000 patient years (5). Conditions such as underlying joint pathology, a background of a systemic disease and compromised immune status, predispose patients to higher risks of developing septic arthritis. The risk factors for septic arthritis are listed in page 3 (6). Septic arthritis can affect any age group but it is common at extremes of ages, and the incidence in male and female patients is equal (7).

Table 1.1 Differential diagnosis of septic arthritis

Infective	Septic arthritis (bacterial, fungal, parasitic)
	Osteoarticular Tuberculosis
	Cellulitis
	Lyme disease
Degenerative	Osteoarthritis
Inflammatory	Psoriatic arthritis
	Rheumatoid arthritis
Crystal deposition disorders	Gout
	Pseudogout
Other causes	Haemathrosis
	Trauma
	Bursitis

List of Risk Factors for developing septic arthritis:

- Degenerative joint disease
- Rheumatoid arthritis
- Corticosteroid therapy
- Diabetes mellitus
- Leukemia
- Cirrhosis
- Granulomatous diseases
- Cancer
- Hypogammaglobulinemia
- Intravenous substance abuse
- Renal disease
- Patients undergoing cytotoxic chemotherapy

Patients usually present within two weeks of onset of symptoms, but an infection caused by a low virulence organism will have a comparatively delayed presentation (8). Patients can present with any or a combination of the cardinal signs of inflammation. These include acute joint pain, swelling around the joint, warmth, erythema, decreased range of motion, fever and generalised malaise (6). Systemic constitutional symptoms such as fever, chills, or rigors are however not always present, with sensitivities of 57%, 27% and 19%, respectively for septic arthritis (9). This sometimes makes a clinical diagnosis difficult, and a high index of suspicion is needed.

Any joint can be affected, with the knee joint (48%) being the most prone to infection (10). Lower limb joints are more vulnerable compared to upper limb and axial skeleton joints (see

Table 1.2 below) (11). Trauma, contiguous spread of infection and diabetes, predisposes patients to unusual presentation of septic arthritis, where small joints of hand and feet can be affected (12). Involvement of the axial skeleton joints such as the spine, sternoclavicular joint and the pubic symphysis have been reported in patients with history of intravenous drug abuse and patients with indwelling catheters (13). Septic arthritis commonly affects a single joint, but oligo-articular or even poly-articular infections do not exclude the diagnosis of septic arthritis, as up to 22% of septic arthritis patients have multiple joint involvement (14).

Table 1.2 Distribution Table of the affected joints

Affected Joint	**Percentage Distribution**
Knee	65%
Hip	12%
Shoulder	6%
Elbow	6%
Wrist	4%
Ankle	4%
Sternoclavicular	3%

Septic arthritis is mostly a clinical diagnosis, but adjuncts do aid in confirming diagnosis. This includes serum markers of inflammation and infection e.g. White Cell Count (WCC), Erythrocyte Sedimentation rate (ESR) and C-Reactive Protein (CRP). Amongst all these markers CRP was shown to be the most reliable compared to ESR and WCC (12). In a retrospective study, significant increases of CRP up to 100 mg/L were shown to only slightly increase the likelihood of septic arthritis (15). Serum procalcitonin, a relatively newer marker of inflammation and infection was shown to have a predictive diagnostic sensitivity and specificity of 65% and 88%

respectively in patients with septic arthritis (16). In a study done by Weston *et al*. (1999) in the United Kingdom only 24% of patients with confirmed positive synovial cultures had positive bacterial identification in their blood cultures, and in 9% of the patients with a clinical diagnosis of septic arthritis a positive blood culture was the only source of bacterial identification (12).

Synovial fluid microscopic and macroscopic analysis are useful tools in diagnosing joint sepsis and crystal induced arthropathies such as gout and pseudogout (17). Microscopic analysis should always be coupled with synovial fluid culture, as gram staining alone is only positive in 50% of the cases (12). Synovial WCC of greater than 50 000 cells/mm^3 is suggestive of septic arthritis, however lower levels do not exclude the diagnosis of septic arthritis (9). Given the pathophysiology of septic arthritis these biochemical derangements in synovial fluid tests are expected, decreased synovial fluid glucose level, raised lactate dehydrogenase and raised protein levels, but however, low sensitivity and specificity limit the usefulness of these tests (9). There is currently not enough clinical evidence to support the use of blood-culture bottles over conventional agar culture in an attempt to increase diagnostic yield (18). Polymerase chain reaction (PCR), a process of identification and amplification of genetic material has recently found use in confirming diagnosis of joint infections where antibiotics are administered before arthrotomy or culture results are negative in clinically confirmed cases of septic arthritis (19).

Conventional radiographs done in 2 orthogonal planes are used in conjunction with clinical examination as the first form of radiological investigation in septic arthritis, but radiographs are less effective in early joint infection as they may show no changes except soft tissue swelling (20). Late presentation of septic arthritis may present with Phemister's triad on radiographs. These includes joint space narrowing, marginal subchondral bone erosions, and peri-articular osteopenia (20). Ultrasound has been used extensively in the diagnosis of musculoskeletal

infections. Absence of joint effusion on ultrasound has been shown to have a high negative predictive value for septic arthritis. Although the presence of an effusion is not specific for septic arthritis (21). Magnetic Resonance Imaging (MRI) may be useful in cases where joints are deep seated and diagnosis is unclear. MRI may show complex joint effusions with changes in signal intensity in both T1W and T2W images. Other associated MRI changes include synovial thickening, peri-synovial edema and capsular pouching. The absence of effusion on MRI does not exclude the diagnosis of septic arthritis (22).

Septic arthritis shows a typical increased radionuclide uptake in all 3 phases (the perfusion, blood pool, and osseous phase) of ^{99m}Tc-diphosphonates scintigraphy scan, the image is in keeping with the hyperemic synovial vessels. Radionuclide imaging can be useful in early septic arthritis where radiological changes are not yet present (23).

Septic arthritis is triggered when bacteria are introduced into the sterile joint and synovial fluid. Hematogenous spread of bacteria following a period of bacteremia is the most common route leading to septic arthritis (6). Less common routes by which bacteria can be introduced into joints include joint aspiration procedures, penetrating injuries and blunt trauma to the joint without a break in skin continuity (24). Synovium that lines joints is well vascularized but lacks the protective basement membrane, this pre-disposes joints to hematogenous bacterial seeding (25).

Gram positive bacteria are responsible for the majority of septic arthritis cases, this is attributed to gram positive species' abilities to bind with the host's connective tissue and extracellular matrix proteins (7). *S. aureus*' ability to be the most common cause of septic arthritis is enhanced by its microbiological characteristics (7). Specific genes that code for proteins which are used as receptors have been identified in *S. aureus* species responsible for the destructive septic arthritis. These features coupled with the ability of *S. aureus* to survive inside neutrophils and other cells

of inflammation makes it a difficult bacterial infection to treat (26). Introduction of bacteria into a patient's joint leads to an inflammatory response. Bacterial components such as the cell wall, adhesins, toxins and enzymes trigger this response (27). Introduction of the foreign material into the joint triggers the host immune response, but it is the host's response which causes most of the damage associated with joint infection (28). The body responds to the presence of bacteria and bacterial components with hyperplasia of synovial lining cells, migration of inflammatory cells into synovium and synovial fluid leading to the typical purulent synovial fluid of septic arthritis (29). Inflammatory cells release proteases, cytokines, interleukins and tumor necrosis factor that directly or indirectly cause cartilage destruction and inhibition of new cartilage formation (6). Joint infection and the inflammatory process associated with it, leads to an increase in joint fluid causing increased intra-articular pressure hampering blood flow to the joint and peri-articular structures. This leads to cartilage and synovium ischemia (25).

Generally, any bacteria can cause septic arthritis. Table 1.3 shows the most common micro-organisms isolated in a study conducted at Steve Biko Academic Hospital in Pretoria, South Africa. The study group included 125 patients with the diagnosis of septic arthritis (30).

Table 1.3 Organisms isolated in 125 cases of septic arthritis in adult patients

Organisms	**No. of Isolates**
Gram positive	**42**
Sthaphylococcus aureus	20
Coagulase negative staphylococcus	11
Streptococcus pneumniae	1
Alpha-haemolytic streptococcus	5
Beta-haemolytic streptococcus	5
Gram negatives	**29**
Acinetobacter baumannii	4
Klebsiella pneumoniae	4
Klebsiella oxytoca	2
Enterobacter spp	5
Eschericiae coli	4
Serratia marscence	1
Proteus mirabilis	1
Proteus vulgaris	1
Pseudomonas aeruginosa	6
Pseudomonas stutzeri	1
Other	**9**

Both local and international studies agree that S. *aureus* is the most prominent pathogen causing septic arthritis with incidences as high as 44% (10, 31, 32). The proportion of cases caused by *S. aureus* in rheumatoid arthritis patients is even higher reported at 75% (33). *Streptococcus* species are the second most common pathogen causing septic arthritis (approx. 28%) with *S. pyogenes* being the most common of the *Streptococcus spp*. (6, 32). *MRSA* is a difficult bacteria to treat and accounts for 5.00 – 25% of bacterial septic arthritis cases (34). Gram negative bacilli joint infection occurs in 14 – 19% of all septic arthritis cases and is commonly associated with conditions such as urinary tract infections, intravenous drug abuse and skin infections (6, 35). *P. aeruginosa* and *E. coli* are the two most common gram negative species (35, 36). Systemic

micro-biological infections like diarrhea can pre-dispose patients to uncommon micro-organism septic arthritis such as *Shigella spp., Salmonella spp., Campylobacter spp*. or *Yersinia spp.* (37). Gonococcal septic arthritis is a rare disease except in the United States where the incidence of Gonococcal infections in general was shown to have increased between 1997 – 1999 by 9% to a level of 133, 2 cases per 100 000 per year (38). Septic arthritis caused by multiple bacteria occurs in approximately 10% of cases (6). Literature is generally in agreement that the most common pathogens causing septic arthritis being *S. aureus* and *Streptococcus spp.*, but there are multiple case reports of rare pathogens e.g. *Corynebacterium striatum* causing shoulder septic arthritis; *Fusobacterium necrophorum* causing septic arthritis in patients with Lemierre syndrome which classically is described as pharyngitis, septicemia and internal jugular vein thrombosis (39, 40). A very rare cause of septic arthritis caused by *Sphingomonas paucimobilis* has been reported in an immuno-competent patient. This bacterium is found in soil, drinking water and even in hospital equipment such as nebulizers and ventilators and has been shown to have high antibiotic resistance (41).

Treatment

Urgent removal of purulent material from the joint and empiric antibiotic treatment is the mainstay of treatment in septic arthritis. Septic joints can be drained either by closed means using needle decompression, or surgically by means of arthrotomy or arthroscopy. There are no studies that show the effectiveness of a specific method of joint drainage over another (42-45). If left untreated septic arthritis causes cartilage destruction, joint space narrowing, subchondral bone loss, peri-articular ligament disruption and occasionally sinus tract formation (46). Septic arthritis is a medical emergency. Inadequate or inappropriate treatment may lead to irreversible joint damage and thus substantial morbidity and mortality (47-49). Reported septic arthritis mortality rates range from 4 to 42%, with poly-articular septic arthritis having mortality rate values as high

as 50% (31, 47, 50). In the acute phase of the infection, the use of splints to prevent flexion contracture deformity is critical as patients prefer to flex their joints. This flexed position of comfort increases joint space, therefore, reducing intra-articular pressure and pain (51).

Initial antibiotic of choice in treatment of septic arthritis is empiric, based on the most common pathogens in that community and according to patient specific risk factors. That particular choice is later modified guided by microbiological gram stain and culture results (49). The British society of rheumatology guidelines for the management of the hot swollen joint in adults suggests intravenous treatment for two weeks then oral treatment for four weeks (18).

A 10-year review of empiric antibiotic use in treatment of septic arthritis done in Switzerland showed that Amoxicillin/Clavulanate or Cefuroxime would have been an appropriate antibiotic in 85% of large joints and only 75% of small joints infections (52). In other studies, the clinical importance of community acquired *MRSA* in causing septic arthritis was highlighted and that empiric antibiotic cover aimed at *MRSA* should be considered (53). In the Pretoria study, *S. aureus* was isolated in 25% of the cases and the use of Cloxacillin as empiric antibiotic treatment was only effective in 32% of the cases (30).

The most common pathogen causing septic arthritis differs from one geographic region to another and varies per patient's specific risk factor profiles; hence the need for each centre to regularly assess common pathogens causing septic arthritis and their antibiotic sensitivities cannot be over-emphasised.

1.1 Research Aim and Objectives

Since the management of septic arthritis includes empiric antibiotic treatment that is later changed according to microbiological results, it is important for each centre to determine the most common pathogens and their antibiotic sensitivities. This will better guide treatment protocols with regards to the use of empiric antibiotics. The aim of this study was to determine common pathogens at Chris Hani Baragwanath Academic Hospital. The research specific objectives were as follows:

1. To document all pathogens found in cases of septic arthritis
2. To determine antibiotic sensitivity of the pathogens
3. To make recommendations towards empiric antibiotic treatment of septic arthritis in adult patients

Chapter 2 - Methodology

The study was an observational retrospective analysis of results in all patients who had a clinical diagnosis of septic arthritis that and were taken to theatre for an arthrotomy. The study was conducted at Chris Hani Baragwanath Academic Hospital, over a period of four years (09 April 2010 to 28 December 2014).

Data collected included admission white cell count, ESR, CRP and post-operative synovial fluid microbiological analysis results

2.1 Study population

The study population included all adult patients who were admitted with a diagnosis of septic arthritis and taken to theatre for an arthrotomy between 09 April 2010 and 28 December 2014. Chris Hani Baragwanath Academic Hospital is the third largest hospital in the world with 3200 beds. The hospital is in the Soweto area of Johannesburg, South Africa. It is one of the 40 Gauteng provincial hospitals, is financed and run by the Gauteng Provincial Health Authorities. It is a teaching hospital for the University of the Witwatersrand Medical School. It serves the community of Soweto which has a population of approximately 1.3 Million per census 2011 and is a referral hospital for other areas of South Africa and Southern Africa (54,55) .

2.2 Inclusion criteria

The inclusion criteria for this study included:

- All patients who were admitted with a clinical diagnosis of septic arthritis taken to theatre for an arthrotomy
- Patients 18 years and older

2.3 Exclusion criteria

The exclusion criteria for this study included:

- All paediatric patients (younger than 18 years)
- Patients with joint replacements
- All patients found in theatre register that had no records and results available at the laboratory database

2.4 Data collection procedure

All patients with a clinical diagnosis of septic arthritis are exclusively managed by the Orthopaedic department. Septic arthritis is mainly a clinical diagnosis. When patients are diagnosed, blood samples are taken for serum WCC, ESR and CRP which are used as adjuncts in diagnosis as well as to serially monitor response to treatment. All Patients with a clinical diagnosis of septic arthritis are then taken to theatre for a formal joint arthrotomy and debridement. Arthroscopy and needle decompression as methods of either diagnosis or treatment are not used in our centre. In theatre, the surgeon collects joint fluid and synovium which is sent to the Microbiology laboratory for gram staining, culture and antibiotic sensitivity tests. Post initial arthrotomy patients are placed on empiric Cloxacillin treatment while awaiting microbiology results to guide further antibiotic choice.

Theatre registries were used to find all patients who had surgical debridement of their joints. Patients' names and Hospital file numbers were used to request blood and microscopy results from the National Health Laboratory Services (NHLS). Results received from the laboratory were compared to initial theatre registries list sent and all patients not appearing on the list of results received from the laboratory were excluded from the study. A data collection sheet was used that did not include any patient identification data (see Appendix **C**).

2.5 Data analysis

Measurement of central tendencies were used to analyse the frequency, mean and standard deviation of the demographic characteristics, WCC, CRP, ESR as well as the type of bacteria cultured from the laboratory and their sensitivities and resistance to antibiotics usually used in treating septic arthritis. The level of significance was measured by using the Chi-square and the Fischer's exact test to determine the association between the sensitivity and resistance of specific antibiotics used on specific bacteria. One-way ANOVA was used to determine the significance difference between the bacteria and the age of the patients. All data analysis was carried out using the IBM SPSS 23.0 ®.

2.6 Ethics

The study was approved unconditionally by the Human Research Ethics Committee (Medical), Faculty of Health Services, University of the Witwatersrand (Clearance certificate no. M140975, Appendix **A**).

Chapter 3 - Results

3.1 Results

3.1.1 Demographics

The theatre registries had a total of 136 patients that had arthrotomies of the joints; of those patients submitted to the laboratory only 82 patients had records and results according to laboratory data. A total of 54 patients were excluded due to unavailability of results during that four-year period between April 2010 and December 2014. Results were not available for 54 patients, and these were excluded from the study. Most patients (43%) were between the ages 34 and 49 years. Figure 3.1 below shows a graphical representation of the age distribution of the patients.

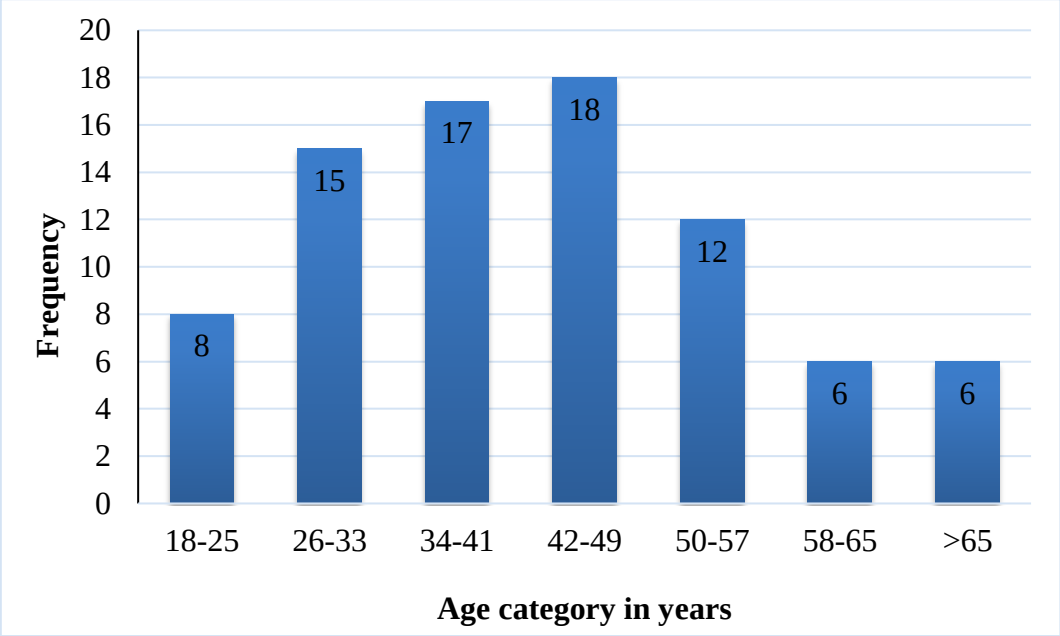

Figure 3.1 A graphical illustration of the age distribution of the 82 patients categorised between 8-year periods

The age groups from 26 years to 49 years accounted for 61% of the patients in our study. The age range of the patients in this study was 18 – 68 years with a mean age of 44.14 ± 12.56 years.

3.1.2 Bacteria species recorded from the laboratory

The laboratory had recorded a total of 203 laboratory results belonging to 82 patients as identified by their hospital numbers, 28 different types of bacteria were identified. The different bacteria isolated were then divided into four broad groups based on their gram staining characteristics, i.e. gram positive, gram negative and mycobacterium species. Figure 3.2 graphically shows the results of gram staining. There is a predominance of gram positive 55% (n = 112) over gram negative 40% (n = 81) species and Mycobacterium species at 5% (n = 10).

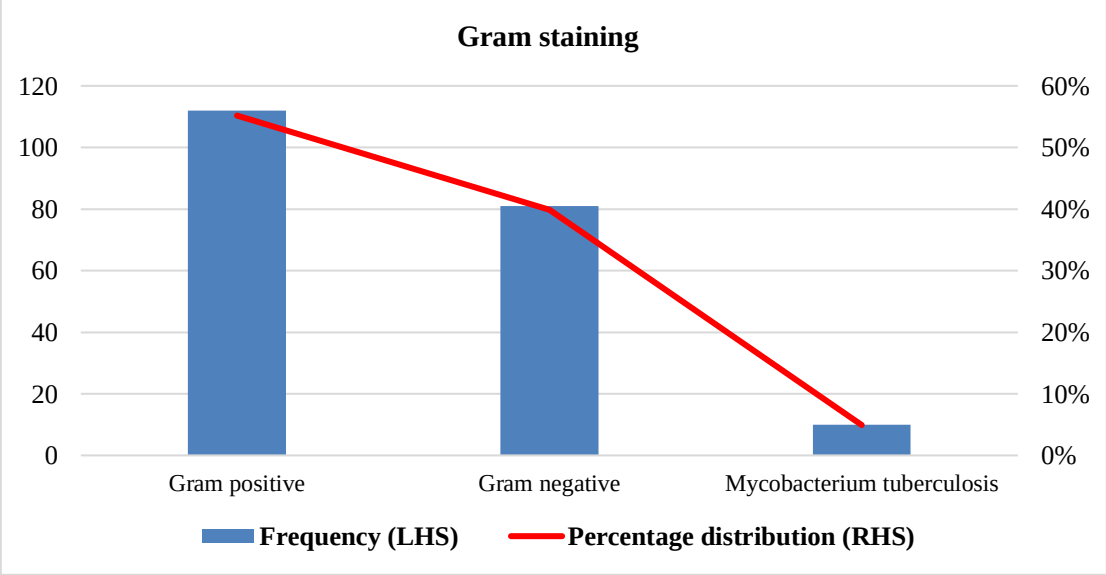

Figure 3.2 A graphical representation of the gram staining results

Further analysis of the culture results revealed a total number of 28 different types of bacteria and the frequency of the specific isolated bacteria is outlined in Table 3.1 below. Of the 82 patients

taken to theatre for arthrotomies, 45 patients (55%) had multiple arthrotomies. Twenty-nine of those 45 patients (64%) with multiple arthrotomies had a change in the bacteria isolated from the index and a subsequent arthrotomy, which might signify hospital acquired infections. Our results had no cases where no growth was reported and no fungal infections were reported.

Table 3.1 Distribution table of bacterial isolates from the laboratory culture results

Bacteria name (*N* = 203)	**Frequency (*n*)**	**% distribution of bacteria**
Staphylococcus aureus	58	29%
Pseudomonas aeruginosa	18	9%
Escherichia coli	16	8%
Acinetobacter baumannii	15	7%
Methicillin-Resistant Staphylococcus aureus	14	7%
Mycobacterium tuberculosis complex	10	5%
Proteus mirabilis	10	5%
Coagulase negative staphylococcus	6	3%
Enterococcus faecium	6	3%
Klebsiella species	6	3%
Enterococcus faecalis	5	2%
Streptococcus agalactiae	5	2%
Streptococcus pyogenes	5	2%
Enterobacter species	4	2%
Enterobacter cloacae	3	1%
Klebsiella pneumoniae	3	1%
Streptococcus pneumoniae	3	1%
Viridans streptococcus	3	1%
Citrobacter koseri	2	1%
Staphylococcus epidermidis	2	1%

Table 3.1 Continues - Distribution table of bacterial isolates from the laboratory culture results

Bacteria name (*N* = 203)	**Frequency (*n*)**	**% distribution of bacteria**
Streptococcus group B	2	1%
Enterobacter aerogenes	1	0.5%
Haemophilus parainfluenzae	1	0.5%
Klebsiella oxytoca	1	0.5%
Serratia marcescens	1	0.5%
Staphylococcus haemolyticus	1	0.5%
Streptococcus anginosus	1	0.5%
Streptococcus species	1	0.5%

S. aureus accounted for 29% of the total bacteria isolated from laboratory records. Also, *P. aeroginosa, E coli* and *A. baumannii* account for 9%, 8% and 7% respectively of the total bacteria isolated.

The isolated bacteria were further grouped into species and the results showed that the *Staphylococcus spp.* (combined) accounted for 40% of the total bacteria followed by the *Streptococcus spp*. at 10%. Figure 3.3 below shows the distribution of the bacteria species identified from the laboratory report.

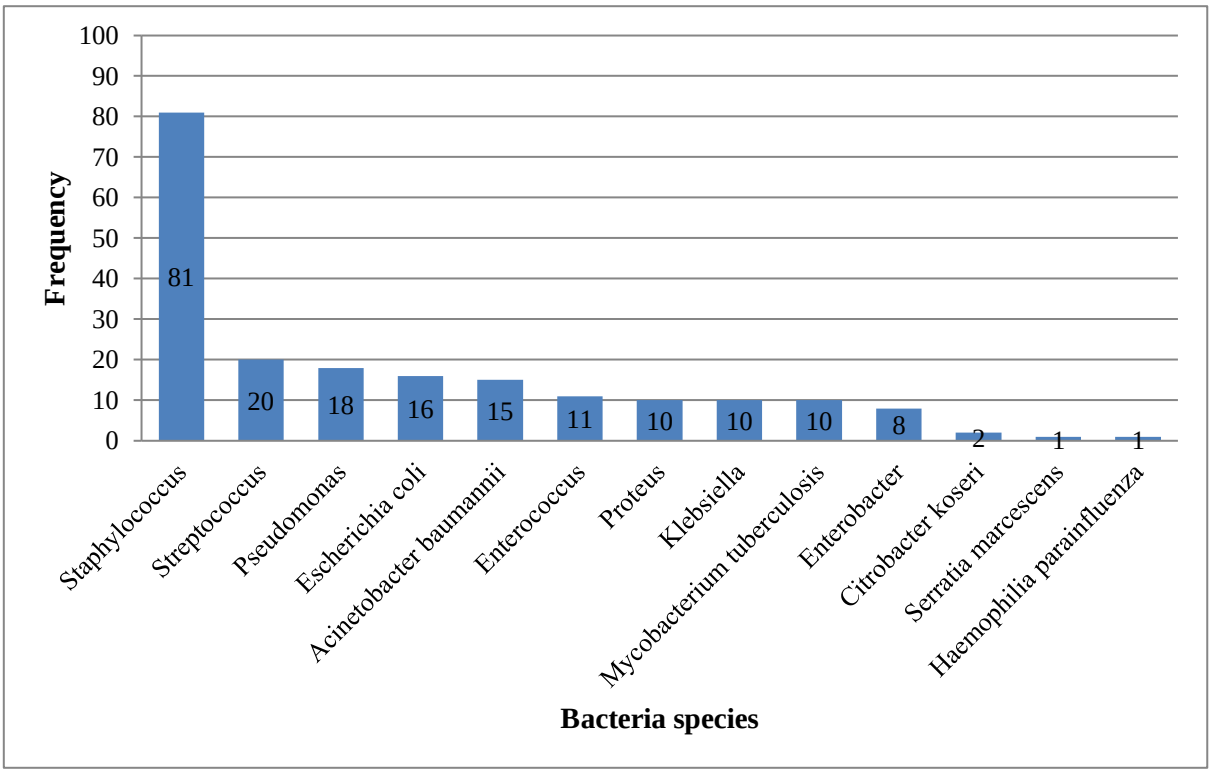

Figure 3.3 A graphical representation of the various bacteria species isolated from the laboratory (with all *Staphylococcus spp*. and all *Streptococcus spp*. combined)

Amongst gram positive bacteria *S. aureus* (52%) and *MRSA* (13%) were the most identified, while *P. aeruginosa* (22%) and *E. coli* (20%) were the most identified gram-negative bacteria. Tables 3.2 and 3.3 below show the distribution of gram-positive and gram-negative bacteria respectively.

Table 3.2 Distribution table of the gram-positive bacterial isolates

Gram Positive Bacteria (*N* = 112)	**Frequency (*n*)**	**% distribution**
Staphylococcus aureus	58	5%
Methicillin-Resistant Staphylococcus aureus	14	13%
Coagulase negative staphylococcus	6	5%
Enterococcus faecium	6	5%
Enterococcus faecalis	5	4%
Streptococcus agalactiae	5	4%
Streptococcus pyogenes	5	4%
Streptococcus pneumoniae	3	3%
Viridans streptococcus	3	3%
Staphylococcus epidermidis	2	2%
Streptococcus group B	2	2%
Staphylococcus haemolyticus	1	1%
Streptococcus anginosus	1	1%
Streptococcus species	1	1%

Table 3.3 Distribution table of the gram-negative bacterial isolates

Gram negative bacteria (*N* = 81)	**Frequency (*n*)**	**% distribution**
Pseudomonas aeruginosa	18	22%
Escherichia coli	16	20%
Acinetobactre baumannii	15	19%
Proteus mirabilis	10	12%
Klebsiella species	6	7%
Enterobacter species	4	5%
Enterobacter cloacae	3	4%
Klebsiella pneumonia	3	4%
Citrobacter koseri	2	3%
Enterobacter aerogenes	1	1%
Haemophilus parainfluenzae	1	1%
Klebsiella oxytoca	1	1%
Serratia marcescens	1	1%

3.1.3 Antibiotic sensitivity and resistance

3.1.3.1 Staphylococcus species

Staphylococcus species was the most common bacteria identified. From the records and as shown in Figure 3.4 below, *Staphylococcus sp.* had 100% sensitivity to Fusidic acid, Linezoloid and Vancomycin. The *Staphylococcus sp.* showed the most resistance towards Penicillin at 90%. *Staphylococcus* species had a total of 75% sensitivity to cloxacillin.

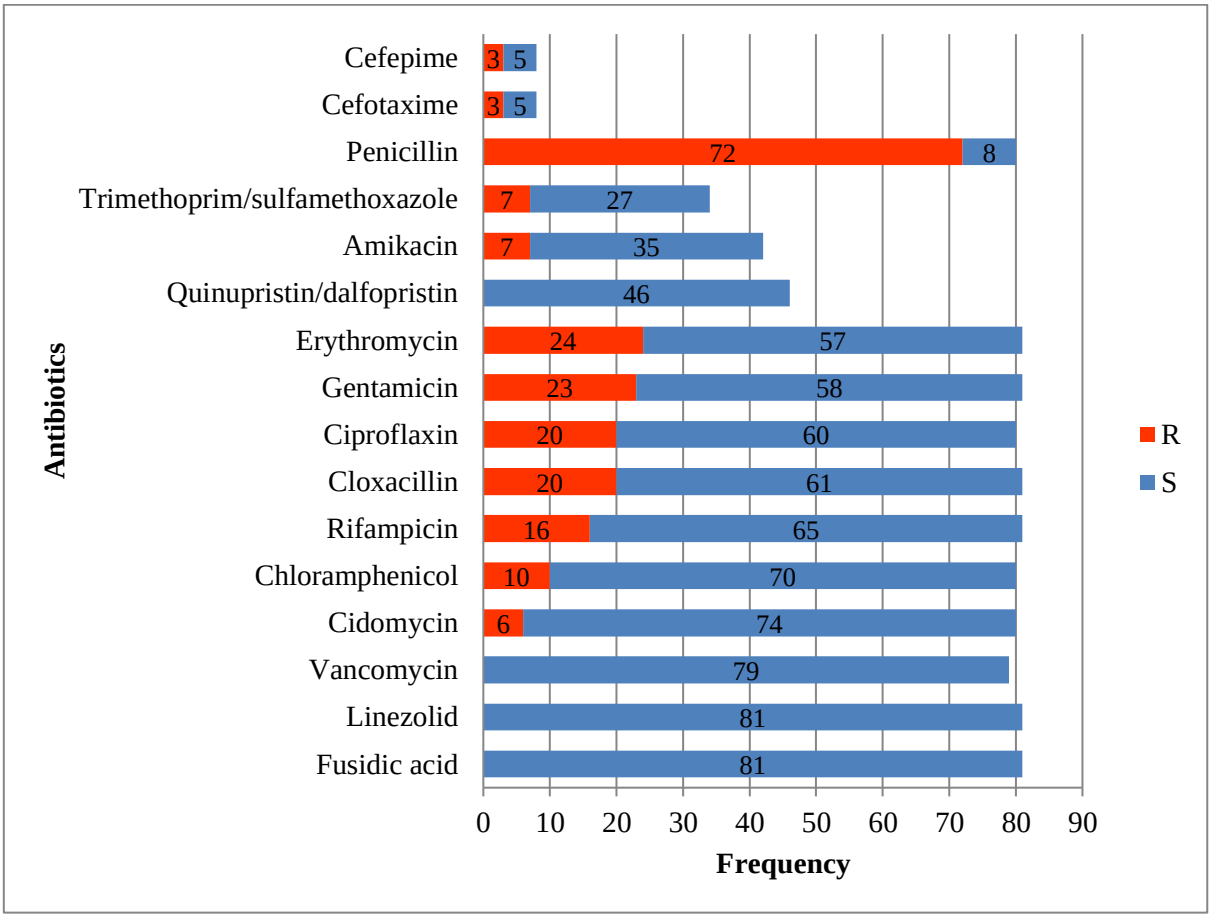

Figure 3.4 A graphical illustration of the sensitivity and resistance of the combined *Staphylococcus* species to antibiotics

3.1.3.2 S. aureus and MRSA

The results of the sensitivity and resistance of antibiotics to the two most common *Staphylococcus* species, *S. aureus* and *MRSA*, showed that *S. aureus* was sensitive to Cloxacillin in (95%) cases. MRSA was reported in 14 cases and as expected there was 100% resistance to cloxacillin. Both *MRSA* and *S. aureus* showed high sensitivity to Linezoloid, Fusidic acid and Vancomycin as shown in Table 3.4 below. *S. Aureus* had a very high resistance to Penicillin (89%) and *MRSA* showed absolute resistance to Penicillin. Cloxacillin was appropriate as treatment in 75% of all *Staphylococcus spp.* cases which translates to only 30% cover of all the bacteria involved in this study (see Figure 3.4).

Table 3.4 Specific sensitivity and resistance of antibiotic to *S. Aureus* and *MRSA*

	***Staphylococcus aureus* (*n*)**		***MRSA* (*n*)**	
Antibiotic	**Resistance**	**Sensitivity**	**Resistance**	**Sensitivity**
Amikacin	0	27	6	5
Chloramphenicol	3	54	6	8
Ciprofloxacin	4	53	14	0
Gentamicin	7	51	13	1
Clindamycin	0	57	6	8
Erythromycin	7	51	14	0
Fusidic acid	0	58	0	14
Linezoloid	0	58	0	14
Cloxacilin	3	55	14	0
Penicillin	51	6	14	0
Rifampicin	3	55	10	4
Trimethoprim/sulfamethoxazole	6	23	-	-
Quinupristin/Dalfopristin	0	28	0	14
Vancomycin	0	58	0	12

The Chi-square results used to determine the level of association between resistance and sensitivity of specific antibiotic to *S. aureus* showed that there was a significant difference in all the antibiotics used for *S. aureus.* This bacterium, *S. aureus* showed a significant sensitivity to all other antibiotics used except for Penicillin where a significant resistance was noted ($p < 0.001$).

MRSA showed a significant level of resistance to Gentamicin ($p < 0.001$). Table 3.5 below outlines the Chi-square results of the significant difference between the sensitivity and resistance of bacteria to antibiotics tested for *S. aureus* and *MRSA*.

Table 3.5 An association between antibiotic sensitivity and resistance of *S. aureus and MRSA*

	Staphylococcus		***MRSA***	
Antibiotic	**X^2**	***p*-value**	**X^2**	***p*-value**
Amikacin	-	-	0.09	0.76
Clindamycin	-	-	0.29	0.59
Gentamicin	33.38	< 0.01	10.29	< 0.01
Rifampicin	46.62	< 0.01	2.57	0.11
Chloramphenicol	45.63	< 0.01	0.29	0.59
Ciprofloxacin	42.12	< 0.01	-	-
Erythromycin	33.38	< 0.01	-	-
Cloxacilin	46.62	< 0.01	-	-
Penicillin	35.53	< 0.01	-	-
Trimethoprim/Sulfamethoxazole	9.97	< 0.01	-	-

3.1.3.3 Streptococcus species

The *Streptococcus sp.* is the second most reported bacteria in this study and as shown in Figure 3.5 below. The *Streptococcus sp*. showed no resistance to both Vancomycin (100%) and Linezolid (100%). The highest resistance recorded for *Streptococcus sp.* was to Tetracycline at 33%.

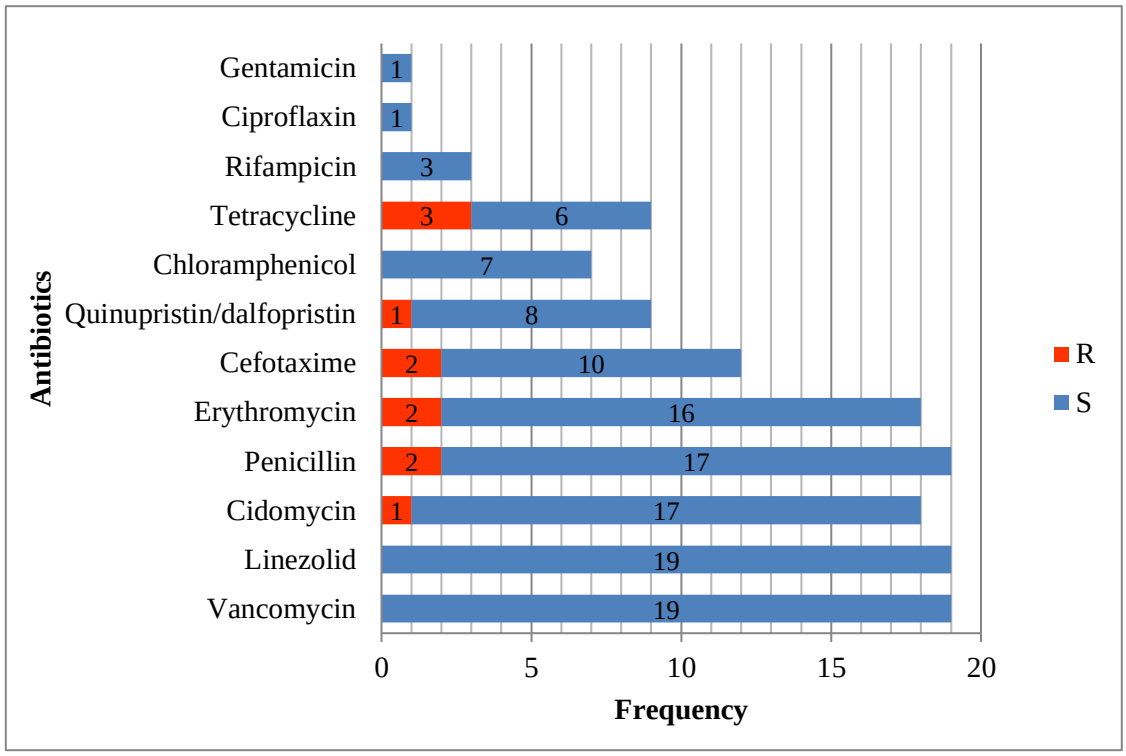

Figure 3.5 A graphical illustration of the sensitivity and resistance of *Streptococcus* species to antibiotics

3.1.3.4. Pseudomonas species

The *Pseudomonas sp.* was the most common group of gram negative bacteria and they showed high sensitivity to Amikacin (100%) and between 93 and 94% sensitivity to Ciprofloxacillin, Imipenem, Cefepime, Cefotaxime, Tobramycin, Meropenem and Gentamicin. *Pseudomonas sp.* showed 100% resistance to Tetracycline and Trimethoprim-sulfamethoxazole as shown in Figure 3.6 below.

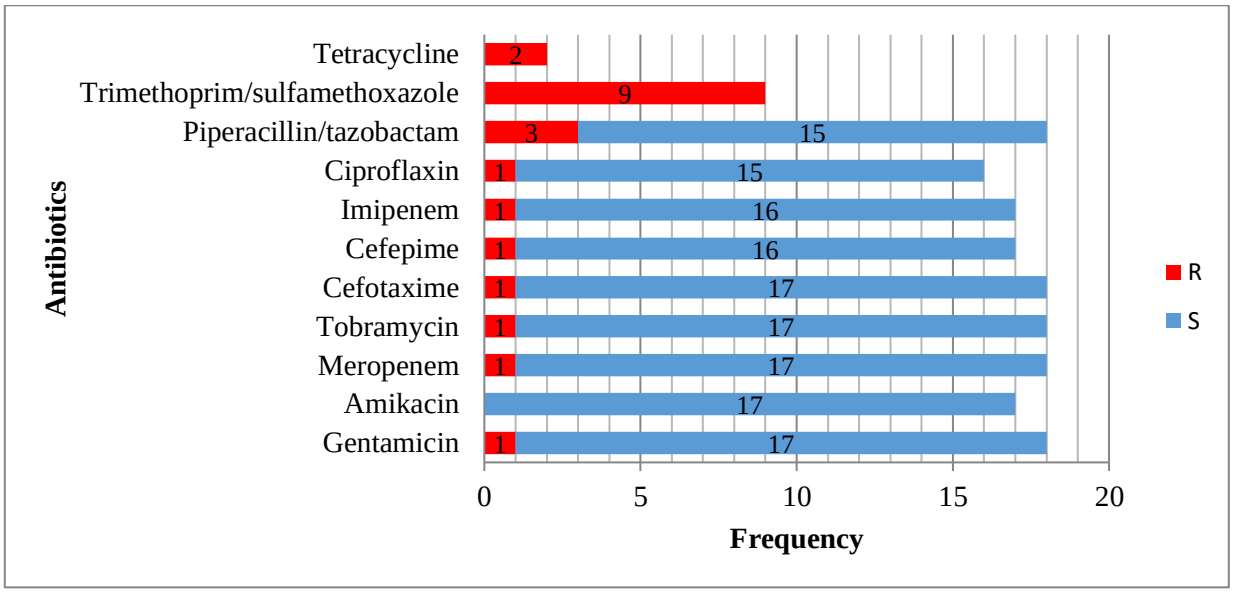

Figure 3.6 A graphical illustration of the sensitivity and resistance of *Pseudomonas* species to antibiotics

3.1.3.5. Escherichia coli

The *E. coli* bacteria were most sensitive to Piperacilin-Tazobactam (94%), Impenem (94%) and Meropenem (94%). The bacterium *E. Coli* was most resistant to Ampicillin (73%) as illustrated in Figure 3.7 below.

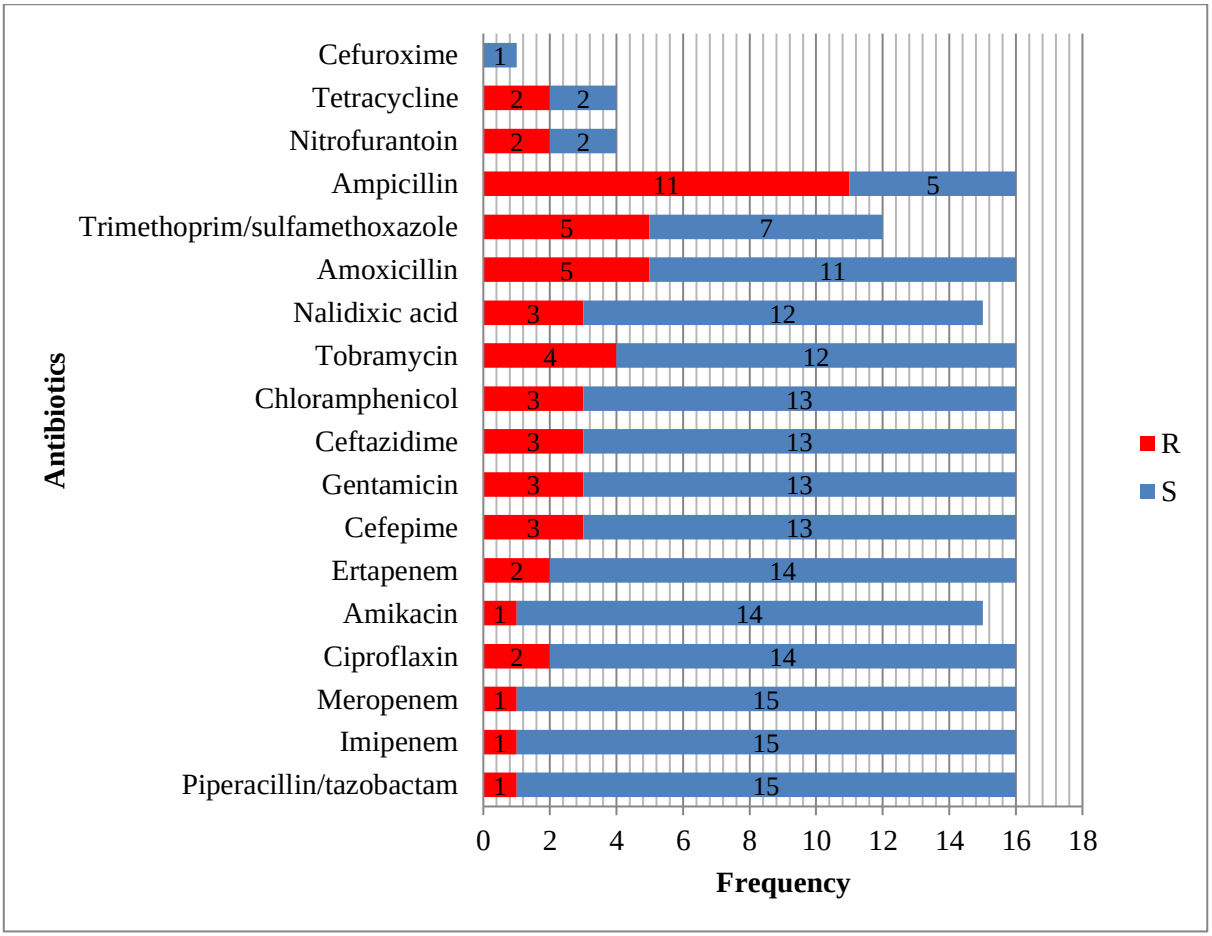

Figure 3.7 A graphical illustration of the sensitivity and resistance of *E. Coli* bacteria to antibiotics

3.1.3.6. A. Baumannii

The bacteria *A. baumannii* were most sensitive to Tobramycin (73%), Gentamicin (67%) and Amikacin (67%). The bacteria were 100% resistant to Tetracycline, Trimethoprim-sulfamethoxazole and Nalixidic acid. Also, the bacteria showed high resistance to Piperacilin/ Tazobactam (92%), Impenem (92%) and Meropenem (80%) as illustrated in Figure 3.8 below.

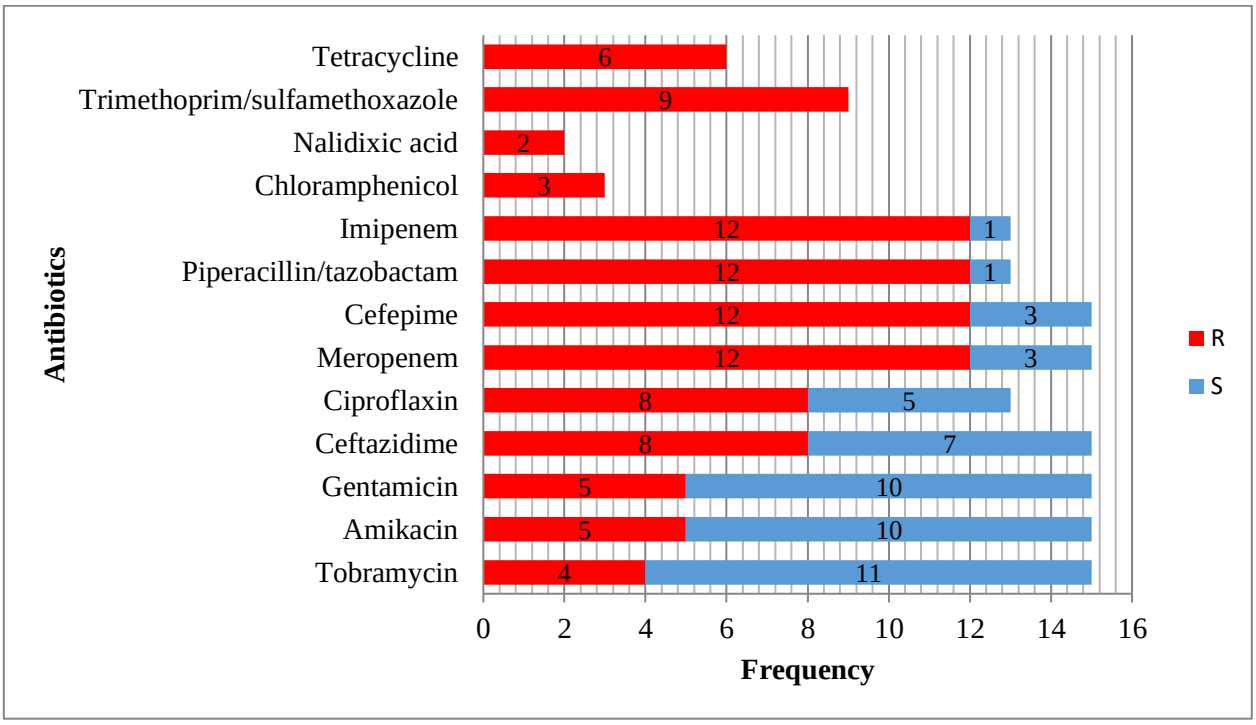

Figure 3.8 A graphical illustration of the sensitivity and resistance of *A. Baumannii* to antibiotics

3.1.3.7. Mycobacterium tuberculosis

Rifampicin was the only antibiotic used to test resistance and sensitivity of *MTB* positive cultures found in this study, 63% cultures were sensitive to the antibiotic as shown in Figure 3.9 below.

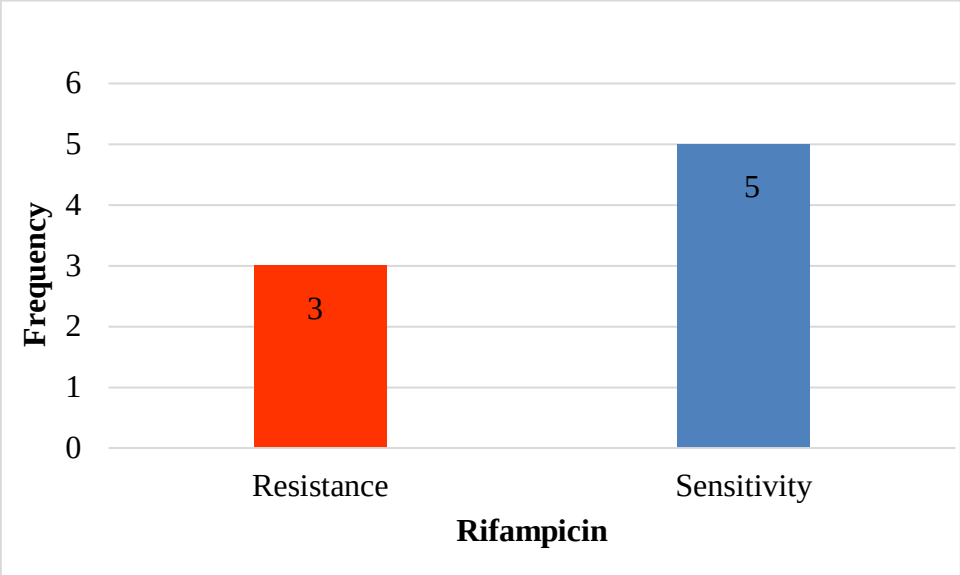

Figure 3.9 A graphical illustration of the sensitivity and resistance of *Mycobacterium tuberculosis* species to antibiotics

3.2 Most effective antibiotic used against gram positive and gram-negative bacteria

The cultured bacteria were grouped into gram positive and gram-negative bacteria according to common microbiological characteristics. Figures 3.10 and 3.11 below demonstrate frequency of sensitivities and resistance that each antibiotic had against the group which it was tested on.

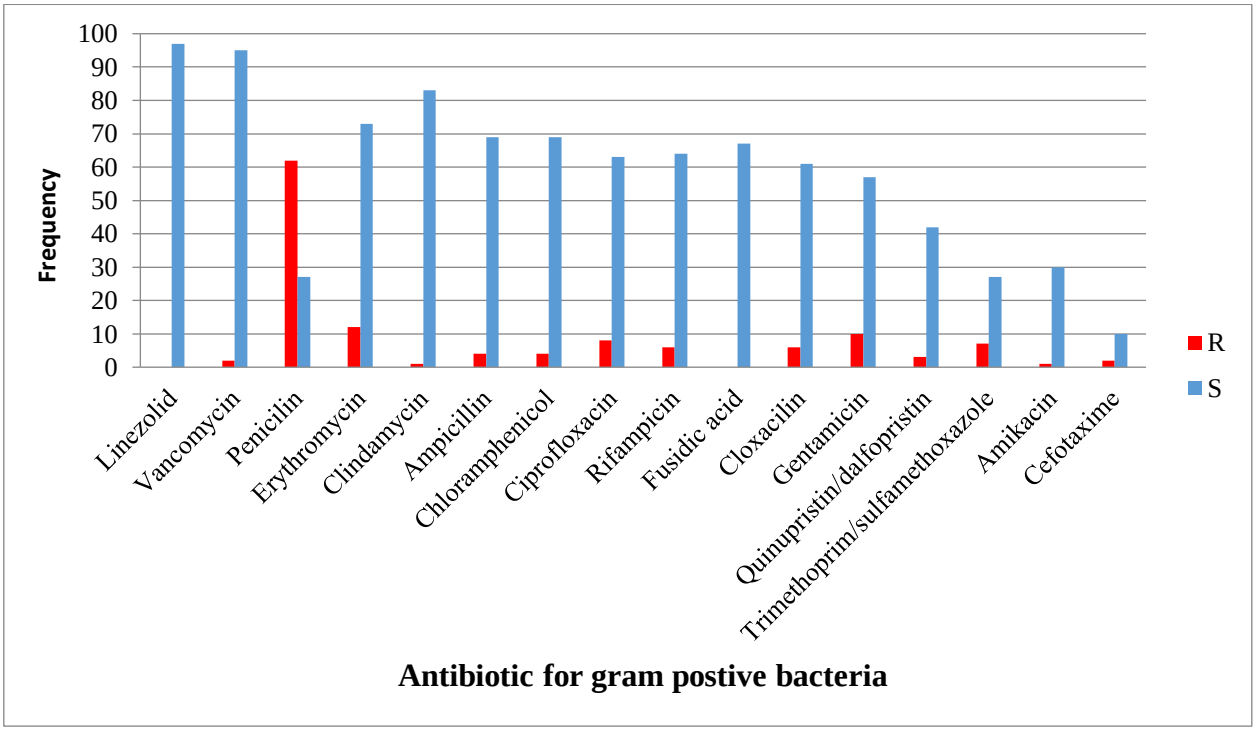

Figure 3.10 A graphical representation of sensitivity and resistance of gram positive bacteria to antibiotics

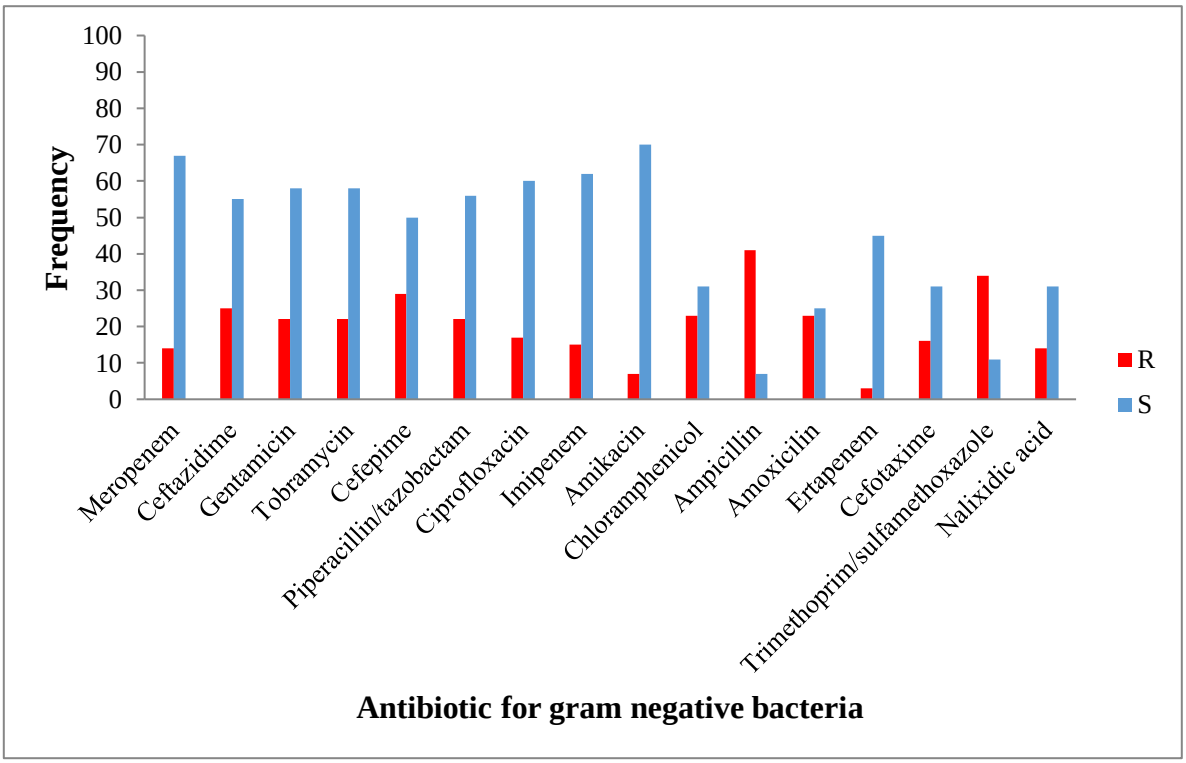

Figure 3.11 A graphical representation of sensitivity and resistance of gram negative bacteria to antibiotics

The above Figures 3.10 and 3.11 respectively showed that Linezolid (97) and Vancomycin (97) were the most effective antibiotic for gram positive bacteria while Meropenem (67), Gentamicin (58), Tobramycin (58) and Ceftazidime (55) were effective for gram negative bacteria.

3.3. Laboratory results

The percentage of cases with reported WCC, CRP and ESR were 19%, 14% and 8% respectively. ESR a marker of inflammation is termed normal if the rate is between 0 − 10mm/hr. The ranges of ESR values recorded in this study are outlined in Table 3.6 below.

Table 3.6 The ranges of Erythrocyte sedimentation rate

ESR value (mm/hr)	**Number of cases**	**Percentage**
0 − 10	1	3%
11 − 100	14	42%
>100	18	55%
Total	33	100%

CRP as another marker of inflammation is reported as normal if found to be less than 10mg/L, patterns in my study are demonstrated in Table 3.7 below.

Table 3.7 C reactive protein values

CRP level (mg/L)	**Number of cases**	**Percentage**
< 10	1	3%
10 − 50	0	0%
51 − 200	18	51%
> 200	16	46%
Total	35	100%

Raised WCC is often used as a marker of infection. Normally in absence of infection values range between (3.9 – 12.6) 10^9/L. Values of WCC in this study are demonstrated in Table 3.8 below.

Table 3.8 White cell count values

White cell count ranges (x 10^9/L)	**Frequency**	**Percentage**
0 − 3.8	2	6%
3.9 − 12.6	27	79%
> 12.6	5	15%
Total	34	100%

Chapter 4 – Discussions

This is the first retrospective analysis to be done at our centre looking at bacteriology of septic arthritis where all surgical treatment of septic arthritis was done by the Orthopaedic department and all specimen and results processed at a single laboratory

Demographics in this study showed that septic arthritis can affect any age group, the majority of our patients (61%) were in the middle-aged group of 26 − 49 years and the mean age being 44 years ±12.56 years. This is in agreement with studies done elsewhere where their mean age among adult septic arthritis patients was 51 years ± 15years (56) .Septic arthritis in advanced age patients has been shown to have adverse outcomes, where death was reported in studies amongst these patients (57) . My study had 15% in the age group 58 years and older and in a similar study done in Nigeria (2013) up to 10% of their patients were above the age of 60 years. Given the figures for high complication rates in this age group, particular attention should be paid to these fragile patients (58).

Gram positive species were the most common pathogens found in my study, this finding is common in most studies.(1, 49, 50). In one particular study the contribution of *Staphylococcus* and *Streptococcus spp.* was as high as 91% which is different from our finding of *Streptococcus* and *Staphylococcus spp*. contributing only 50% of all septic arthritis cases (50).

The predominance of S. *aureus* as a causative agent in septic arthritis has been proven in literature; Ross *et al.* (2005) showed that *S. aureus* caused 44% of cases in their North American study which is in contradiction with our study where we found that only 29% of cases were

caused by *S. aureus*. Our study though, is more similar to a study done in Pretoria, where *S. aureus* caused 33% of all septic arthritis cases (7, 30).

According to the 2006 guidelines on the management of the hot swollen joints in adults with septic arthritis from Britain, it was reported that in patients with no risk factors for atypical organisms, Fluxlocacillin could be used as the most appropriate antibiotic (59). Patient profiling per specific risk factors was not done in this study but Cloxacillin was appropriate as treatment in 75% of all *Staphylococcus spp.* cases which translates to only 30% cover of all the bacteria involved in this study. The use of Vancomycin increases empiric antibiotic cover as it has 47% effectiveness against all isolates. In patients with suspected *Streptococcus* infection use of Penicillin and Erythromycin still provides reasonable cover with 89% and 89% effectiveness against *Streptococcus spp.* respectively. Newer drugs such as Linezolid with 100% effectiveness against gram positive species seem to be superior amongst all antibiotics

Resurgence of resistant strains in each centre warrants frequent assessment of common species and their antibiotic sensitivity. In a study done in Taiwan *MRSA* was found in up to 20% of cases of septic arthritis. In this study *MRSA* only caused 7% of septic arthritis cases, while in the Pretoria study showed that 11% were caused by *MRSA* (30, 61). *MRSA* in all the studies was shown to be exclusively sensitive to Linezolid and Vancomycin. Even though this study showed that *MRSA, S. aureus* and *Streptococcus spp.* all had 100% sensitivity to Vancomycin, the routine use of Vancomycin as a first line antibiotic is not advisable, as it may be associated with decreased clearance of the bacteria and other systemic side effects (61).

According to ministry in department of health the number of people living with HIV increased from 5.48 million to 6.19 million people in the period of 2011 to 2015 (62). This study was not

aimed at determining the impact of HIV on bacteriology of septic arthritis, but Zalavras *et al.* (2006) demonstrated that in patients with HIV infection and low CD4 count the most common pathogen was *Oxacillin-resistant S. aureus* (63). Further studies in our setting are required to understand the prevalence of HIV infection and incidence of resistant strains of *S. aureus*.

Gram negative species account for up to 20% of micro-organisms causing septic arthritis and immune-compromised patients have higher incidence of gram negative micro-organisms, with *E. coli* and *Pseudomonas spp*. being the most common gram negative pathogens. This study showed that 40 % of cases were caused by gram negative bacteria and in agreement with other studies where *Pseudomonas spp.* and *E.coli* were the most common gram negative species (6).Gram negative septic arthritis although rare can be difficult to treat, requiring multiple surgical debridement and appropriate antibiotic treatment (64). Laboratory results showed that gram negative species best responded to Amikacin, Meropenem, and Gentamycin at 87%, 83% and 72% respectively.

Nosocomial infections have been on the rise over the years, infections with bacteria like *A. baumannii* are difficult to treat and have high mortality and morbidity rates (65). *A. Baumannii* are highly resistant to antibiotics possibly due to presence of drug resistant genes (66). In this study, *A. baumannii* was responsible for 7% of cases and as in most studies *A. baumannii* was shown to be a highly resistant bacterium to antibiotics. Bacteria such as *A. baumannii* are difficult to treat with Tobramycin being the only agent providing adequate cover against it at 73%.

In another study done in our centre recently, extra pulmonary tuberculosis infection was shown to have a prevalence of 88.6/100 000 population (54). Ten cases (5%) were caused by *Mycobacterium tuberculosis complex* in this study and 37% of those *Mycobacterium tuberculosis complex* infections showed mono-resistance to Rifampicin. Further studies are required to

investigate prevalence of Mycobacterium tuberculosis complex infections resistance to anti-tuberculosis drugs used.

The use of serum markers of infection and inflammation in confirming diagnosis of septic arthritis has been shown to be unreliable (9). My study shows a slightly different result, of the 33 patients tested for WCC only 27% had raised WCC. CRP was tested in 13 patients and 12 of the 13 patients (92%) had abnormal CRP. ESR was tested in 23 patients and in 95% of those patients ESR was abnormal. The number of patients who had ESR, CRP and WCC tests done was very low, a follow up study might be required to clarify the association between these markers of inflammation and confirmed cases of septic arthritis.

Single surgical debridement was shown to be ineffective in up to 38% of cases in one study. This study showed that more than half (55%) of the patients who were surgically treated for septic arthritis required re-operation. Submission of new specimen with each episode resulted in 64% of a change in the initial bacteria cultured. Indications for re-operation were not objectively described in hospital records, further studies analysing clinical response and need for re-operation may be useful in future.

This study may not reflect the true epidemiology of septic arthritis at Chris Hani Baragwanath Academic Hospital reasons being, firstly septic arthritis is not a notifiable disease and some patients may not be in our records and secondly this retrospective study was dependent on theatre records where it was possible that not all patients were recorded.

Some specimens belonging to patients who were clinically diagnosed with septic arthritis and were taken to theatre for arthrotomies were never recorded at the laboratory site and as a result this poor record keeping, poor specimens handling and processing may have contributed to losses

in patients' information. Furthermore, there was inconsistency on the number of serological investigations and the types of tests done on our patients.

4.1 Future directions

Future Directions: Given the prevalence and ever-increasing incidence of HIV in our communities, further studies can help us understand the relationship between level of immunity amongst HIV positive patients that present with septic arthritis looking at their CD4 count, viral load, HIV clinical staging, use of antiretroviral and if there is a difference in bacteria cultured. The finding of a significant number of patients who had a change in bacteria cultured with multiple arthrotomies can be investigated to understand if it correlates with number of days spent in hospital and if these were nosocomial infections.

Chapter 5 - Conclusion and recommendations.

In this study, gram-positive bacteria were predominant as causative agents of septic arthritis, *Staphylococcus* and *Streptococcus spp.* accounted for 50% of bacteria that caused septic arthritis. Gram negative species accounted for about 40%, although not as common as gram positive species they also contribute to causative agents of septic arthritis and they respond to specific and unique antibiotics.

In patients without specific risk factors use of Cloxacillin as the most appropriate antibiotic for gram positive cover will only be effective in 30% of the cases, we recommend the use of Vancomycin which in our study was shown to have superior cover against gram positive species, renal function and general health status of the patients should be continuously monitored whenever Vancomycin is used in patients with suspected *Streptococcus* infection we suggest the use of Penicillin or Erythromycin. Newer drugs like Linezolid seem to be superior amongst all antibiotics when it comes to gram positive cover but more studies are required before widespread use is suggested. In cases of gram negative septic arthritis our study showed that Amikacin and Gentamycin had the best sensitivity in the laboratory further studies are needed for clinical effectiveness against these bacteria. Bacteria such as *A. baumannii* are difficult to treat with Tobramycin being the only agent providing adequate cover against it. *Mycobacterium tuberculosis* complex should be considered in patients at risk of having TB infection. Treatment for TB infection is unique and over a prolonged period. Follow up of results is very important as in some cases poly-microbial septic arthritis exists which require multiple antibiotic regimens.

The importance of frequent bacteriological profiling in each area cannot be over emphasised. This study showed a difference in bacteria cultured in our area comparted to other centres. In patients who needed multiple debridements it is important to follow up microbiological results as

this might change the initial choice of antibiotic or even imply addition of a totally different antibiotic. Use of serological test may help in the management of septic arthritis but cannot be fully relied onto confirm or dispute the diagnosis.

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Appendices

Appendix A – Human Research Ethics Letter (Medical)

R14/49 Dr KM Matekane

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140975

NAME: (Principal Investigator)	Dr KM Matekane
DEPARTMENT:	Orthopaedics CHBAH
PROJECT TITLE:	Micro -organism causing septic arthritis in adult patients at Chris Hani Baragwanath Academic Hospital
DATE CONSIDERED:	03/10/2014
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Ziyat Mayet
APPROVED BY:	Professor PE Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	05/12/2014

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 Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B – CEO approval Letter (Chris Hani Bara Hospital)

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
IN THE OFFICE OF THE CEO
Enquiries: Ms. Thabile Ndlovu
Tel : (011) 933- 9145
Fax: (011) 938-1005
Email: Thabile.Ndlovu2@gauteng.gov.za

To : Dr. KM Matekane
(M140975)

From : Dr. Sandile Mfenyana
CEO: CHBA hospital

Date : 05 November 2014

Re : Micro-Organisms Causing Septic Arthritis in Adult Patients at CHBAH

Your application to request permission to conduct the study on Micro- Organism Causing Septic Arthritis in Adult Patients at Chris Hani Baragwanath Academic Hospital is approved by the CEO: Dr. Sandile Mfenyana

Hoping that the Institution (CHBAH) will meet the requirements of the study concerned.

Wishing you well in your future endeavors

Regards,

DR. SCB Mfenyana
CEO: CHBA Hospital

Appendix C – Data Collection Form

Micro-Organisms causing Septic Arthritis in adult patients at Chris Hani Baragwanath Academic Hospital	
Hospital number	
Unique patient code	
Age (years)	
Date of operation	
Organism isolated	
Erythrocyte sedimentation rate (mm/hr)	
C reactive protein (mg/dL)	
Serum white cell count	