Antibiotic targeted cement rods in chronic osteomyelitis, short-term outcomes from a level one South African trauma centre

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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

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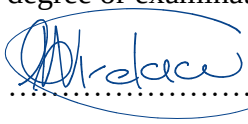
Declaration

I, Caterina Nicolaou, 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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(Signature of candidate)

9th day of September 2022 in Johannesburg.

Dedication

To the humble patients of Chris Hani Baragwanath Academic Hospital; whose gratitude urges us to continue the daily fight.

To my parents who have been my strength and my guiding lights.

For my boys, Andreas and Leandro, who understand, comfort and love me after the long hours of struggle.

Presentations arising from the research project

1. South African Orthopaedic Association (SAOA) conference, Hybrid conference, Cape Town, October 2020
2. Africa Trauma Summit and Conference, May 2021
3. South African Orthopaedic Association (SAOA) conference, Hybrid conference, Cape Town, August 2021
4. University of Witwatersrand, School of Clinical Medicine, Biennial Research Day, Johannesburg, September 2021
5. Wits Orthopaedic Surgery Research Day, Online Conference, November 2021

Abstract

Background: Chronic osteomyelitis requires complex management plans. Meta-analyses and systematic reviews have not found a gold standard of treatment for this disease. However, the literature reviews various treatment options. This study assesses the efficacy of an alternative treatment protocol to what is generally used in South Africa. This treatment protocol involves debridement, reaming and irrigation; as well as targeted antibiotics, used in a cheaply, effectively, and easily made cement rod spacer

Methods: A retrospective record review was performed on 38 patients, diagnosed with chronic osteomyelitis secondary to a long bone fracture, whom were treated via a specified treatment protocol at Chris Hani Baragwanath Academic Hospital between 01 January 2017 and 31 December 2018. This treatment protocol involved staged surgery with the use of antibiotics and antibiotic tailored cement rods. Data were collected and analysed accordingly using Stata 16.0, 2019.

Results: The results indicate that chronic osteomyelitis is most prevalent amongst young males with a median age of 36 years. A multitude of organisms were cultured from bone reamings suggesting targeted antibiotic therapy is required. This treatment protocol demonstrated a 75.7% microbiological resolution to a negative culture. A good clinical outcome of 84.2% overall was demonstrated in terms of sinus resolution, skin changes, pain and function. All inflammatory markers decreased post-treatment with C - reactive protein showing a statistically significant decrease ($p = 0.0043$).

Conclusion: Chronic osteomyelitis remains a complex disease to treat. Our treatment protocol demonstrates favourable microbiological, serological and overall clinical outcomes. Our study highlights antibiotic targeted cement rods as a feasible treatment option in managing chronic osteomyelitis secondary to long bone fractures.

Acknowledgements

Thank you to Dr Juan David Urrea who set out on this project; Dr Allan Sekeitto and Dr Brenda Milner for encouraging me to do the best. To the legendary professors and doctors of Johannesburg and Soweto who inspire us all daily to be better and to push for change for our patients and our communities. We are all puzzle pieces moulded from our experiences with other people. I would like to acknowledge all the people in my larger community for moulding and shaping me. In the words of Professor Bluhmson, the conscience of Bara, “There are no unimportant acts of kindness. Act as if what you do makes a difference. Act as if it were impossible to fail. It is the greatest of all mistakes to do nothing because you can only do a little. Do what you can.”

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Nomenclature

AAOS	American Academy of Orthopaedic Surgeons
CHBAH	Chris Hani Baragwanath Academic Hospital
CRP	C - reactive protein
DRI	Debridement, Reaming and Irrigation
ESR	Erythrocyte Sedimentation Rate
FRI	Fracture related infection
HIV	Human Immunodeficiency Virus
Hb	Haemoglobin
IV	Intravenous
LEFS	Lower Extremity Functional Scale
LMICs	Low- and middle-income countries
MRSA	Methicillin-resistant *Staphylococcus aureus*
PDLLA	Poly (D, L-lactide)
PMMA	Polymethylmethacrylate
S. aureus	*Staphylococcus aureus*
SA	South Africa
WCC	White Cell Count

Chapter 1: Introduction and literature review

1.1. Background

Chronic osteomyelitis secondary to traumatic long bone fractures is a burden on our healthcare system and a cause of long-term morbidity. Treatment strategies currently are lengthy, tedious and expensive requiring prolonged hospitalisation with only moderate outcomes due to the complexity of the disease [1]. This has significant implications for patients especially in a low- to middle-income environment where sole breadwinners cannot be hospitalised for excessive amounts of time [2]. Many patients relapse over time as definitive infection eradication is never certain [2]. This not only causes poor patient satisfaction and outcome, but furthermore an economic strain to our healthcare system.

1.1.1. Definition and classification

Osteomyelitis is an infection of the bone and may be classified based on the mechanism of infection; haematogenous or non-haematogenous; and the duration of illness; acute or chronic [3]. The presence of sequestrum is considered the most appropriate way to classify an infection as chronic [4].

Fracture related infection (FRI), as defined by the consensus meeting in 2018 [5], is a term accepted to encompass; in an uncomplicated manner; all fracture related infections. This definition does not classify infection anatomically or chronologically. The confirmatory criteria for diagnosis of fracture related infection include:

1. Presence of a fistula, sinus or wound breakdown
2. Purulent drainage from the wound or presence of pus during surgery
3. Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens
4. Histopathological presence of microorganisms in deep tissue taken during an operative intervention [5]

Suggestive criteria have also been defined and these require investigations in order to confirm the diagnosis [5]. As this definition is a broad and all-encompassing definition, it is also important to look at a classification system that divides patients into various groups to assess if certain factors may predispose patients to this disease process.

Chronic osteomyelitits has been classified and so divided by Cierny and Mader; who classified osteomyelitis according to the physiology of the host, as well as the anatomic and radiological features [3]. This classification system describes the functional impairment due to the disease, the site of involvement and the extent of bony necrosis [3].

1.1.2. Aetiology and risk factors

Due to bacterial contamination and soft tissue damage incurred with open fractures, patients who sustain such injuries are at a higher risk of developing osteomyelitis [6]. Osteomyelitis can occur in up to 25% of open fractures [3]. The risk of infection in open tibia fractures is twice as high as from other sites [3]. Orthopaedic surgery often involves implantation of foreign bodies during fracture fixation which adds to the promotion of infection in these already at-risk patients. In patients who sustain open fractures, infections occur at a rate of 5% to 33% even though peri operative antibiotics are routinely administered and are effective in reducing infection rates of orthopaedic surgery [6]. This trauma at the tissue implant interface disturbs tissue function and later infection may be caused by bacteria seeded during surgery [7]. Biofilm formation on the implant makes the infection more difficult to eradicate [7].

1.1.3. Impacts of chronic osteomyelitis on our patient population

We focus on Chris Hani Baragwanath Academic Hospital (CHBAH), the largest hospital in the country and the third largest in the world [8]. In the South African setting, at this level one trauma centre located in Johannesburg, one can observe a high volume of fractures [9]. CHBAH surgeons operated on 1126 orthopaedic trauma patients in the first six months of 2019. CHBAH saw 7829 orthopaedic trauma patients in their outpatient clinic in a six-month period in 2019 [9]. This institution further serves a population who suffers the burden of Human Immunodeficiency Virus (HIV) and other co morbidities, putting them at a higher risk of osteomyelitis. This system is overburdened by other acute trauma patients. Another major trauma centre in South Africa (SA) saw 8722 trauma admissions over a five-year period [9]. As a result, there is often no room nor time to truly devote to the lengthy treatment and care of patients with chronic osteomyelitis. Hence there is a desperate need for a successful, cost-effective treatment plan for such patients in our setting.

1.1.4. Treatment

The cornerstones of treatment have been thorough surgical debridement of necrotic bone, large-volume irrigation, and systemic antibiotics [3]. Other key treatment principles of chronic osteomyelitis are improvement of host factors, culture of specimens at the time of surgical debridement, targeted antibiotic therapy, management of the dead space, soft tissue coverage, and bone reconstruction and stabilisation [11]. Increasing evidence suggests that patients with osteomyelitis should be treated in a specialised unit by a multidisciplinary team including infectious diseases specialists and a limb reconstruction surgeon [12].

1.1.5. Current treatment guidelines and trends

Current treatment generally involves complete resection of all the necrotic, non-viable or infected tissues and copious flushing with a total volume of three to nine litres of saline to the affected site which significantly reduces bacterial load [9]. The establishment of adequate blood flow after debridement will allow for effective systemic antimicrobial penetration and infection resolution. The suggested duration of antibiotic therapy varies from four weeks to six months, with treatment adjustment after microbiology analysis and culture thus targeting antibiotic therapy [11]. The suggested initial empiric antibiotic choice is Vancomycin and Meropenem to cover Methicillin-resistant *Staphylococcus aureus* (MRSA) and anaerobes [12].

The dead space post-debridement can be managed with a cement spacer, for example the use of polymethylmethacrylate (PMMA) impregnated with antibiotics. Thermostable Vancomycin, at a dosage of 2 – 4 grams per 40 grams of cement, has been the most commonly used antibiotic [4]. The suggestion to add Rifampicin to another drug with activity against *Staphylococcus aureus* (*S. aureus*) recurs in the literature due to its ability to penetrate the bacterial biofilm. However, Rifampicin should never be used as monotherapy due to the risk of rapidly developing resistance with Rifampicin monotherapy [11].

The Lautenbach technique, developed locally in SA by Professor Lautenbach, is a technique still highly respected and performed in many centres across the world to treat osteomyelitis. The Lautenbach system (Heritage Surgical Products cc) of debridement, irrigation and

reaming (DRI) uses a closed double lumen tube delivering antibiotic locally, followed by suction. This technique was first described in the 1970's [13, 14], and involves debridement, intramedullary reaming and inserting a closed double lumen tube. This double lumen tube allows for delivery of antibiotics locally and allows for cavity analysis via culture sampling. This system, originally showing success rates of 85.2% with no evidence of recurrent infection [14], is still used in centres in SA with no recent studies comparing the technique to other modalities. However, the need for intensive nursing and prolonged hospital stay makes it difficult. It is an expensive and time-consuming technique when compared to many other more convenient antibiotic delivery systems [15].

1.2. Literature review

There is currently no gold standard of treatment in the literature for chronic osteomyelitis. A systematic review done in 2017 by Geurts et al. [2] aimed to identify a standard successful treatment regimen for chronic osteomyelitis in low- and middle-income countries. One thousand, one hundred and seventy-three (1173) patients from Asia and Africa were included from 102 studies [2]. Unfortunately, the overall evidence of the included nine studies was not strong enough to identify the most effective treatment and treatment regimens differed substantially. In all the studies, patients received some form of local surgical intervention; debridement or sequestrectomy. The application of local antibiotic delivery systems varied amongst the studies included in the systematic review. Recovery rates differed between 52.0% and 97.7% [2]. The application of local antibiotic delivery systems varied amongst the studies. This recent and large systematic review could not draw conclusions regarding the most effective treatment, nor could the authors make recommendations on the best suitable treatment of chronic osteomyelitis in low-income countries [2]. This highlights the need for research into the treatment for chronic osteomyelitis especially in low- to middle-income population groups.

1.2.1. Local antibiotic delivery systems

As systemic antibiotics may not achieve effective local concentrations in damaged tissue, [6] the main limiting factor in treatment has been an effective local antibiotic delivery system at the tissue/implant interface. Furthermore, a dead space due to implant removal and necrotic tissue debridement confounds the situation making the area relatively inaccessible to the systemic antibiotics [6]. In recent years, there has been an increase in publications on the use

of various antibiotic delivery devices. These methods include antibiotic loaded bone cement, traditionally PMMA cement and bioabsorbable cements, constructed in various ways. These elude antibiotics over time, achieving high bactericidal local concentrations for an extended period [11,17]. The local antibiotics do not generally enter the systemic circulation in high concentrations thus avoiding the side effects with no or low toxicity levels [16].

Fabricating an antibiotic cement nail/rod can be challenging however, there are various methods making it efficient, reliable and practical [16]. Various antibiotics can be used (rather than the standard Gentamicin) in order to target therapy to the bacteria cultured and still maintain adequate elution rates, and mechanical and thermal stability up to at least 70 degrees Celsius. [17]. PMMA [18], and particularly Palacos R+G cement (Heraeus, bone cement with Gentamicin Sulphate), have been found to be the best carrier material in terms of elution rates and structural support [19].

The literature was reviewed and the application of these antibiotic delivery devices; success rates and how these outcomes were assessed (refer to Table 1.1).

Table 1.1: Outcome assessments and success rates following the application of various antibiotic delivery devices

Article	Follow-up time frame	Patient number	Outcome assessment	Success rate
Wasko et al. [20]	6 years	10	Union on X-rays	100% (but all patients underwent additional surgeries in 6 years)
Kanakaris et al. [4]	21 months	25	CRP, X-rays, clinical findings (not defined)	96%

Reily et al. [21]	Minimum 6 months	41	Clinical examination and serological markers	76%
Marais et al. [24]	Minimum 12 months follow-up	28	Impairment: Quick Dash scoring system upper limb AAOS lower limb outcomes Remission and suppression: Score set out by An et al.	96.2%
Wentao et al. [18] (animal study)	6 to 12 weeks	Not defined	X-ray and histopathology	Not defined
Lucke et al. [7] (animal study)	6 weeks	10 in trial group (total 30 in 4 different comparison groups)	X-rays Hb and WCC Negative culture conversion	Not defined. Scored separately for each parameter
Sancineto et al. [23]	Minimum 12 months	19	Negative cultures	100%

Cho et al. [24]	(Negative culture conversion rate of the intraoperative culture results at the end of treatment was used rather than follow-up)	40	Negative culture	85%
Wu et al. [25]	2 years	36	Infection cure, resolution of clinical signs ESR, CRP Bone union on X-ray LEFS leg function questionnaire functional leg activities (self-reported questionnaire)	97% 82%
Conway et al. [26]	Minimum 12 month follow-up	110	Union on X-rays CRP, ESR Clinical findings (sinus, cellulitis)	95%

Key:

CRP = C - reactive protein

AAOS = American Academy of Orthopaedic Surgeons

Hb = Haemoglobin

WCC = White cell count

ESR = Erythrocyte Sedimentation rate

LEFS = Lower Extremity Functional Scale

Studies have shown good outcomes with antibiotic delivery devices as assessed by clinical findings, X-ray analysis and serological markers on follow-up which averages six to twelve months. A study of 24 patients used a combination of a Reamer Irrigator Aspirator system and administered pathogen-specific antibiotics locally using impregnated cement rods as well as systemic antibiotics for six to eight weeks. At 21 months follow-up, 23 patients (96%) had no recurrent infection as assessed by clinical findings, C-reactive protein (CRP) levels and X-ray analysis [4]. A retrospective review performed at a level one trauma centre in Baltimore in 2016 by Reilly et al. analysed 41 patients treated from 2000 to 2011. These patients were treated with intramedullary nails for tibia fractures and subsequently needed antibiotic nails. Thirty-one patients (76%) had no evidence of infection, as assessed by clinical examination and serological markers, after treatment with a custom-made antibiotic nail [21].

Studies have also shown good outcomes when looking at culture conversion to a negative culture at final surgery or post-treatment. In a study of 40 patients done by Cho et al. in 2018 [24], antibiotic cement-coated hinged threaded rods were used as a temporary intramedullary spacer in 22 of the patients, and 18 of the patients had a single rod to treat intramedullary long bone infections and septic non-union. Eighty-five percent (85%), 34/40 cases, of patients converted to a negative culture after initial debridement and antibiotic rod placement [27].

Well controlled animal studies have also shown good outcomes in study participants when assessing X-rays, serological markers, microbiology and histopathology changes over a follow-up period of six to twelve weeks post-treatment. Lucke et al., from Humboldt University of Berlin, performed an *in vitro* study on rats to evaluate the efficacy of biodegradable, Gentamicin-loaded poly D, L-lactide (PDLLA) coating of Kirschner wires in preventing implant related osteomyelitis [7]. This was assessed by contaminating the medullary cavities of tibiae in 30 rats with *S. aureus* and osteomyelitis was observed in all

these rats. Comparison groups were used whereby titanium Kirschner wires implanted were either uncoated (group II), coated with PDLLA (group III), or coated PDLLA 10% Gentamicin (group IV) (with a thin PDLLA coating to serve as a drug carrier providing the antibiotic at the tissue/implant interface). A control group (group I) was also used. Follow-up was over six weeks whereby weekly X-rays, blood counts, body temperature and weight were assessed. Signs of infection became radiologically and microbiologically evident by two weeks. Radiographic assessment found a significant reduction in bony destruction throughout the follow-up period of animals in group IV of the study. Cultures of implants of this group also showed significantly reduced bacterial growth compared to the other cohorts [7].

1.2.2. Current treatment at our centre

Due to our overburdened system in the orthopaedic trauma unit, patients with chronic osteomyelitis wait for formal and definitive treatment. Most of these patients are in the interim treated ineffectively with oral antibiotics and dressings until an available theatre date could be found for debridement, reaming and irrigation (DRI) or an available hospital bed for other treatment. In 2017, our institution began following a different treatment plan. This protocol involved staged surgery with removal of hardware, debridement, reaming and irrigation, and microbiological analysis. This was followed by the insertion of an intramedullary antibiotic cement rod (*i.e.* a local antibiotic delivery device). The treatment was complete once intraoperative reaming cultures were negative or once a marked clinical improvement was achieved. Treatment failure was defined as a persistence of infection and positive culture and non-union despite the use of multiple antibiotic cement rods and oral or intravenous antibiotics. A detailed treatment protocol is presented in Chapter 2.

1.3. Study relevance/justification

Systematic reviews [2, 6, and 28] highlight the lack of a gold standard of therapy for chronic osteomyelitis, as well as the lack of a treatment protocol that is inexpensive and shows good outcomes specifically in medium- to low-income settings such as ours. More recently, the use of various antibiotic delivery systems has been investigated showing good success rates. An integrated approach is required for the management of chronic osteomyelitis of long bones in adult patients in the developing world [22]. Based on this review, we endeavoured to analyse the use of antibiotic tailored cement rods; inexpensively made in theatre; combined with a

course of antibiotics; as well as a staged treatment plan in a low- to medium-income socio-economic area; used at CHBAH.

1.4. Study aim and objectives

Aim:

To assess the short-term outcomes with staged surgery following the use of tailored antibiotic cement rods in the treatment of chronic osteomyelitis, secondary to traumatic long bone fractures.

Objectives:

- To assess the microbiologic resolution of disease from culture results taken at the time of initial surgery, removal of hardware and debridement, and at the time of final surgery (removal of final antibiotic cement rod).
- To assess the clinical improvement, in terms of skin changes and sinus resolution, at three months follow-up.
- To assess biochemical improvement with the use of inflammatory markers (CRP and ESR) and White Blood Cell counts post-treatment and at three months.

Chapter 2: Methodology

2.1. Research question

Is staged surgery with Debridement, reaming and irrigation (DRI), targeted antibiotic cement rods and concomitant intravenous or oral antibiotic therapy an effective treatment plan for chronic osteomyelitis?

2.2. Research design

This was a retrospective study.

2.3. Research site

The study was performed using patients who were treated for chronic osteomyelitis at CHBAH.

2.4. Research population

The study population consisted of 38 patients who underwent staged surgery with the use of antibiotics and antibiotic tailored cement rods for the treatment of chronic osteomyelitis secondary to traumatic long bone fractures in the Orthopaedics Department at CHBAH between 01 January 2017 and 31 December 2018.

2.5. Selection criteria

2.5.1. Inclusion criteria:

- Adult patients aged 18 years and older who had previous hardware *in situ* for the treatment of a traumatic injury and have subsequently developed chronic osteomyelitis secondary to this hardware (specifically, lower limb long bone fractures and osteomyelitis *i.e.* tibia and femur)

2.5.2. Exclusion criterion:

- Patients with chronic osteomyelitis resulting from haematogenous spread or other causes
- Patients who were non-compliant with their treatment and who were inadequately followed-up

- Patients who did not complete the treatment protocol

2.6. Treatment protocol

The treatment protocol included:

1. Removal of hardware and DRI; obtaining cultures from this initial procedure and initially empiric cover with Vancomycin IV.

2. Insertion of an antibiotic targeted cement rod and repeat DRI.

3. Administration of targeted antibiotics IV or orally for a six-week duration (antibiotics given and inserted discussed with microbiology and infectious diseases to ensure the most effective coverage and duration of treatment).

4. Repeat DRI, cultures analysis and exchange cement rod at six weeks.

5. Removal of cement rod six weeks later and final DRI or insertion of an antibiotic coated cement locking nail (for patients who had mechanical instability).

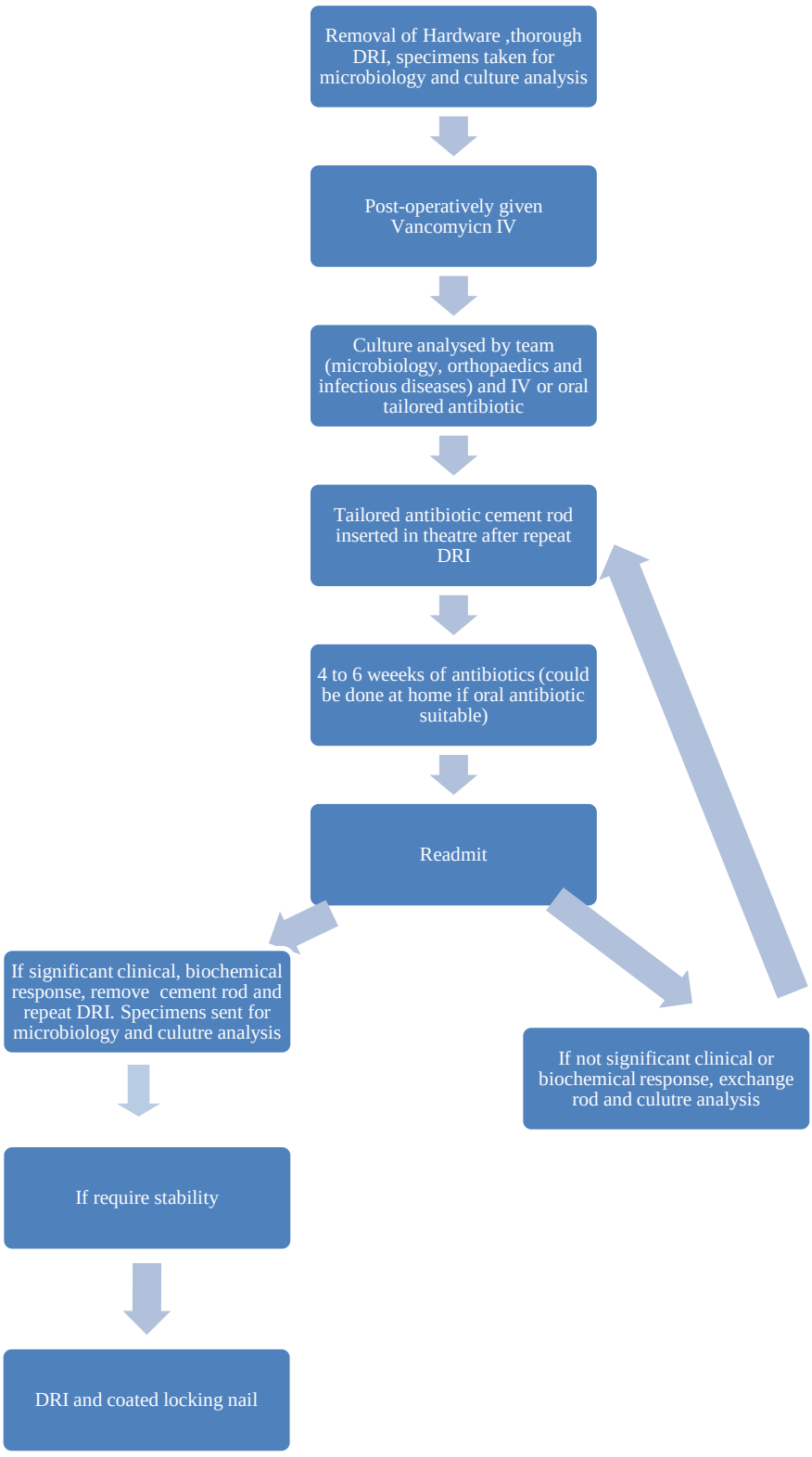

Figure 2.1: Flow diagram of staged treatment protocol

The cement rods were quickly and cheaply assembled in theatre under sterile conditions using the equipment as illustrated in the image below.

Figure 2.2: Sterile equipment needed for antibiotic cement rod

The equipment used to assemble the rods included: reamers for DRI, sterilised olive tip guidewire, bolt cutter, mixing bowl to mix antibiotic powder and powder cement, cement polymer, thermostable silicone tubing of adequate diameter (10mm diameter internally or 12mm diameter internally for a coated locking nail or for a femur), catheter tip syringe and with scissors (to insert cement into tubing), blade to remove silicone tubing from cement rod once hardened, pliers to bend and bury wire proximally.

The same two surgeons assembled the cement rod for each case. Palacos R+G cement (Heraeus Medical GmbH, Germany) was used which already contains 4g Gentamicin. Vancomycin was always added to every rod. Further antibiotic was added to the cement, all in powder form, depending on the sensitivity of the culture. The selected antibiotic was discussed with microbiology as well as infectious diseases to ensure optimal treatment. The selected antibiotic was always selected only if considered, by literature review, to have the ideal elution kinetics and to be thermostable [17]. 2g Vancomycin plus a maximum of 2g of another antibiotic would be used to not affect stability and achieve effective elution [17]. If the culture was sensitive, and only Vancomycin was required, up to 4g of Vancomycin was added.

Antibiotics were initiated on admission for surgery with empiric Vancomycin IV. Once cultures were analysed, in discussion with microbiology and infectious diseases, the antibiotic was changed to a specific targeted choice which was given for four to six weeks. If possible and available, an oral antibiotic was given. This is in keeping with the suggested guidelines from the Rothman Institute International Consensus Meeting which has found no clear evidence to suggest a longer duration of antibiotics [15]. Furthermore, there is no evidence to support that an intravenous antibiotic is superior to an oral one.

Measurements for the length of the cement rod were assessed pre-operatively or on the table with the leg in external rotation, measuring from medial tibial plateau to the articular surface of the ankle, minus 20mm (5mm from the proximal aspect and 15mm from the ankle joint) [30].

Once everything was prepared, the cement monomer was added to the powdered antibiotic and cement powder mixture. Once sticky, the catheter tip syringe; whose nozzle had been shortened; was used to insert the cement into the silicone tubing (similar to a cement gun). Once tubing was full of cement, the prepared guide wire was inserted with its tip below the cement mantle. The cement was left to harden and silicone tubing sliced with a blade and removed leaving a smooth, perfectly circular cement rod which allowed for easy insertion and removal.

Figure 2.3. Removing silicone from the cement rod

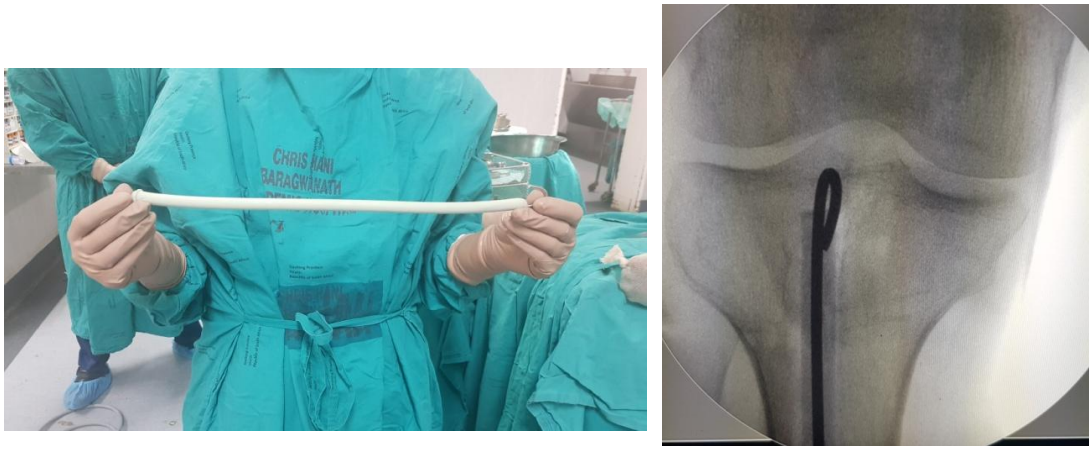

Figure 2.4: (Left) Guide wire olive tip distally and bent proximally for easy removal, (Right) X-ray of proximally buried rod

On average, patients would require three surgeries with the first two on the same admission. Firstly, the DRI and culture collection; and secondly, a subsequent rod insertion on the same admission. This was followed by a third surgery of the rod removal. If a patient had at this point a slow or poor clinical and biochemical response, an exchange rod would be done in one setting instead of just a rod removal. If a patient had to this point a good clinical and biochemical response however, had a positive virulent growth on removing the rod, then another rod insertion was planned for shortly after. Patients who required fracture stabilisation after treatment of the osteomyelitis were then given a final antibiotic coated locking nail as the cement rod itself may not have offered the full mechanical stability required.

Figure 2.5: Coated locking nail

A 12mm internal diameter of silicone tubing used to coat a locking nail prepared in the same technique. Caution was taken to prevent cement from entering locking holes by temporarily filling them with bone wax.

2.7. Data collection

Ethics clearance was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M200911) (Appendix A), as well as from the hospital CEO (Appendix B) prior to data collection. The variables listed below were collected directly from patient records and files, and were captured on a data collection sheet (Appendix C). Follow-up visits clinical findings had been documented and collated by the orthopaedic registrars at the time of follow-up; all following the same structure of questions and assessments *i.e.* clinical resolution of sinus and skin changes, pain, and function. This collated data from the time of follow-up was then retrospectively reviewed and added to the data collection sheet.

2.7.1. Variables

The following variables were collected from patients' clinical records (see Appendix C):

- Demographics: Age, gender, co-morbidities, cigarette use
- Initial diagnosis, surgery and date (e.g. open tibia fracture, tibial nail)
- Date of chronic osteomyelitis diagnosis and classification (Cierny-Mader Anatomical / Host Classification)
- Septic control surgery date and culture obtained (*i.e.* removal of hardware and DRI)
- Date of tailored rod insertion, antibiotic used in rod and antibiotic given parenterally or orally
- Subsequent surgeries *i.e.* removal of rod, exchange rod, whether definitive surgery was needed for bone stability and functionality
- Clinical outcome at three months follow-up: clinical resolution of sinus and skin changes, pain, and function (clinical outcomes were defined as follows:
    - Good: defined as complete resolution of sinus drainage, wounds, skin changes, pain and function
    - Average: defined as partial resolution of sinus drainage, wounds, skin changes, pain and function
    - Poor: defined as incomplete or no resolution of sinus drainage, wounds, skin changes, pain and function)

- Microbiology results at the initial surgery follow-up surgeries and at the final surgery
- Biochemical markers on presentation before initial surgery and at follow-up

2.8. Data analysis

Stata 16.0, 2019 was used for data analysis. The medians, frequencies and *p*-values of the data were calculated. The Fisher's exact test and Spearman's rank test were used to calculate the *p*-values (a p-value < 0.05 was considered as statistically significant).

Chapter 3: Results

Thirty-eight (38) patients met the inclusion criteria for the study. Ten patients were excluded due to incomplete records of biochemical markers, treatment deviating from the set protocol, or suffering from haematogenous cause of osteomyelitis.

3.1. Demographics

The graphs below illustrate the demographics of the patients included in the study. Of the patients included, 84.2 % (n=32) were male with a male to female ratio of 5.3:1.0 (Figure 3.1). The median age of the study group was 36.9 years with the majority of patients falling into the age category of 31 to 40 years (Figure 3.2). With regards to co-morbidities, 51% of the patients had no co-morbidities, and the most common co-morbidity was HIV (27%) (Figure 3.3). In addition, 26% (n=10) of the patients did not know their HIV status or refused testing during treatment. This is a significant proportion when looking at the number of patients who had a positive HIV status (29%, n=17) (Figure 3.4). Fifty-three percent (53%) of the patients were smokers (Figure 3.5). The majority of the patients treated (74%, n=28) had sustained an open fracture at the time of injury (Figure 3.6). The data are also presented in Table D.1 in Appendix D.

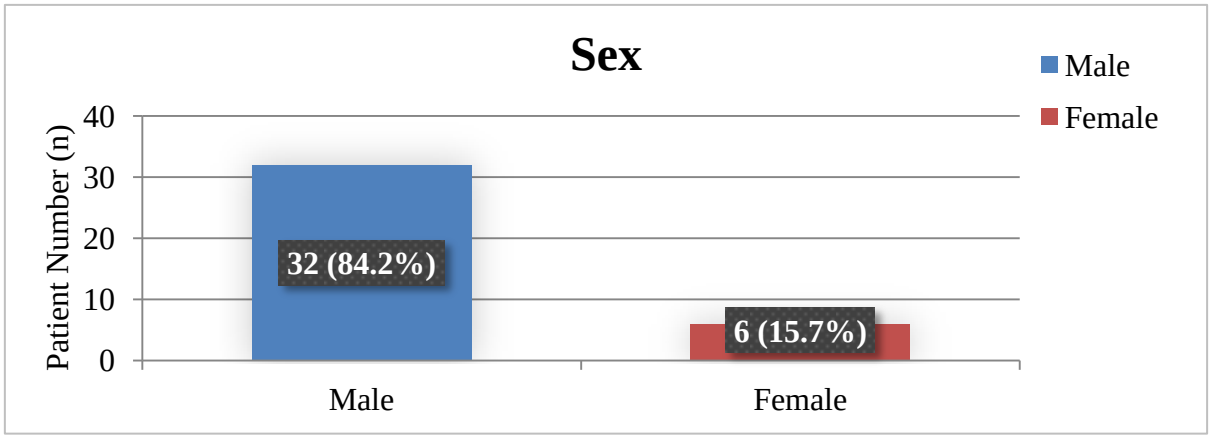

Figure 3.1: Demographics of sex in patient group

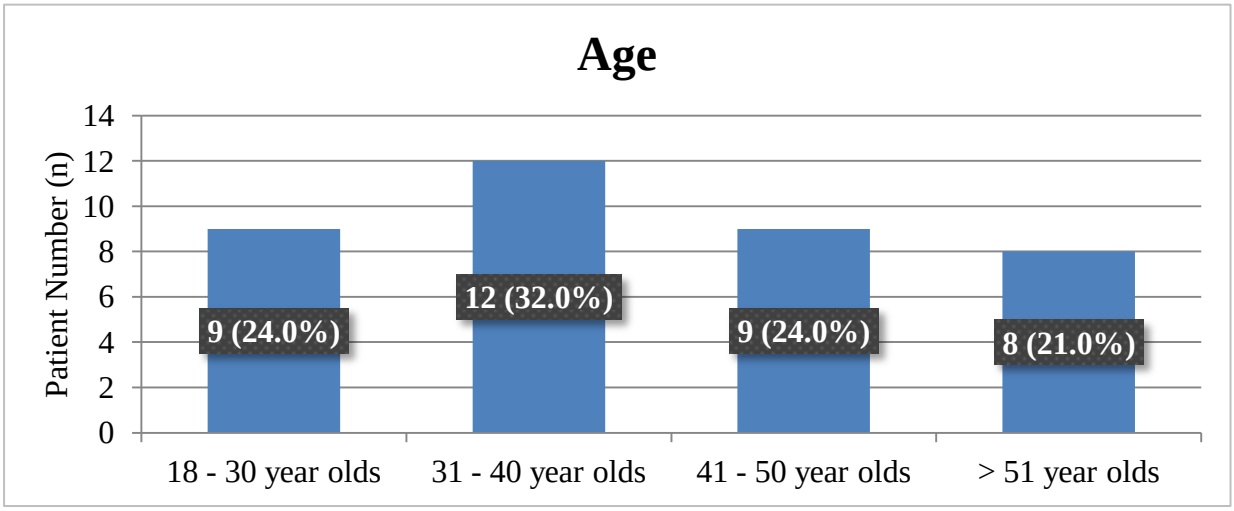

Figure 3.2: Demographics of age in patient group

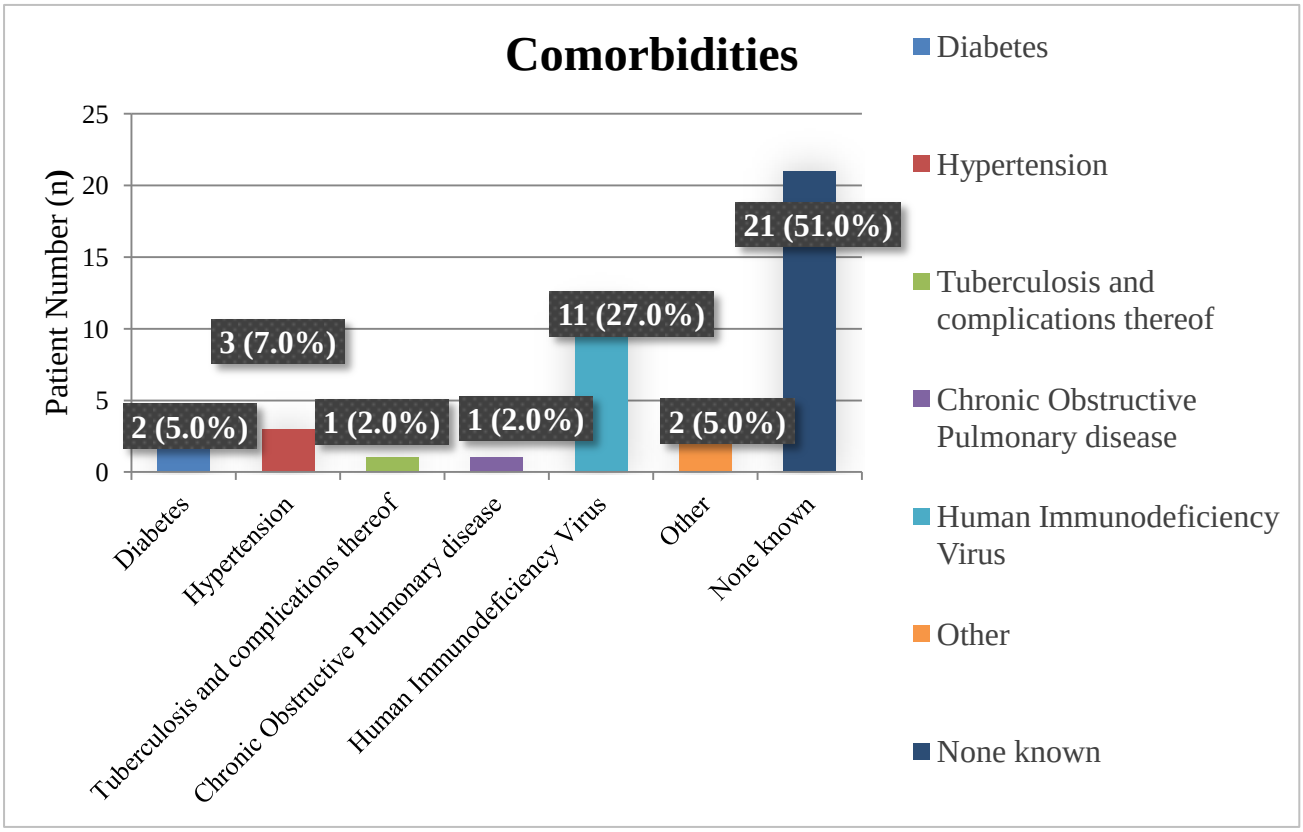

Figure 3.3: Demographics of co-morbidities in patient group

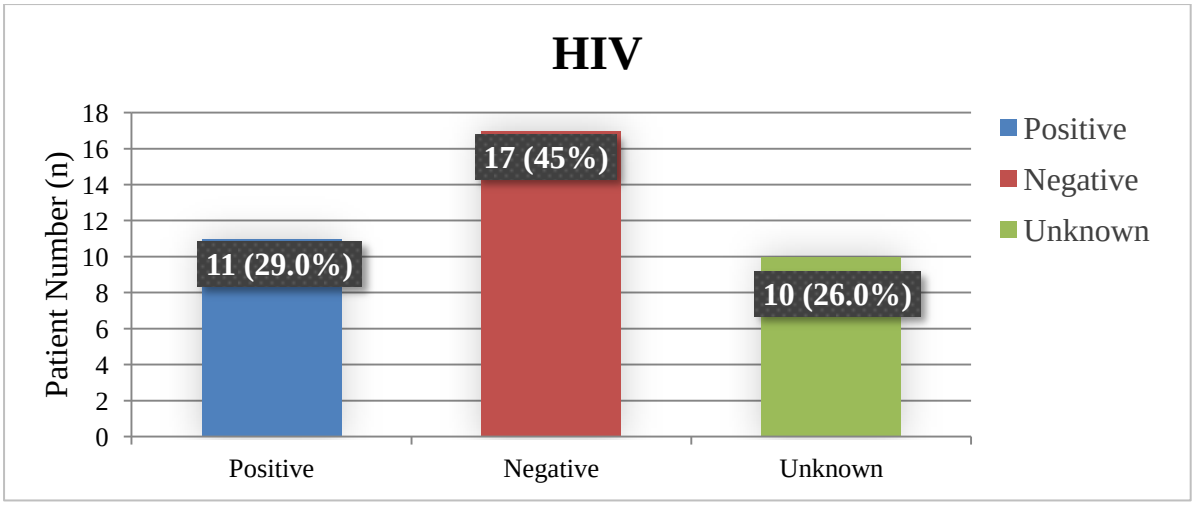

Figure 3.4: Demographics of HIV in patient group

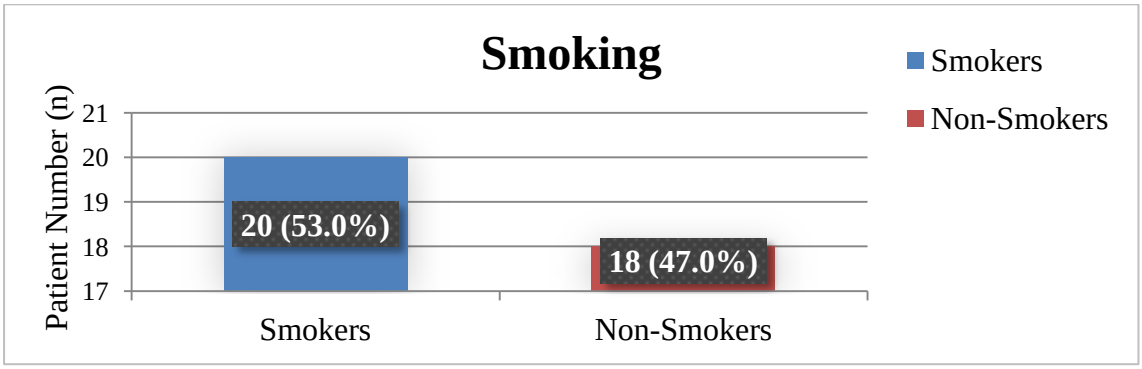

Figure 3.5: Demographics of smoking status in patient group

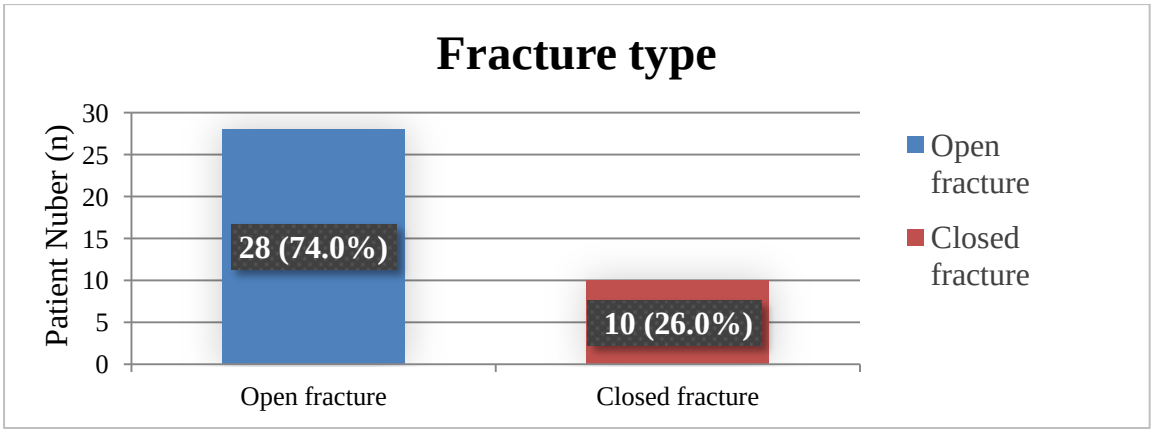

Figure 3.6: Demographics of initial fracture type in patient group

As all patients in the study filled confirmatory criteria for fracture related infection (FRI) [5], they were rather classified and divided using the Cierny and Mader classification of chronic osteomyelitis. Seventy-four percent (74%) of the patients were classified as a Cierny-Mader B host (Figure 3.7) however; these patients were not in a poor clinical condition. Furthermore, 42% of the patients were anatomically classified as type 1 chronic osteomyelitis by Cierny-Mader (endosteal disease) and 42% were classified anatomically as type 3 (localised to cortical sequestrum with bone stability).

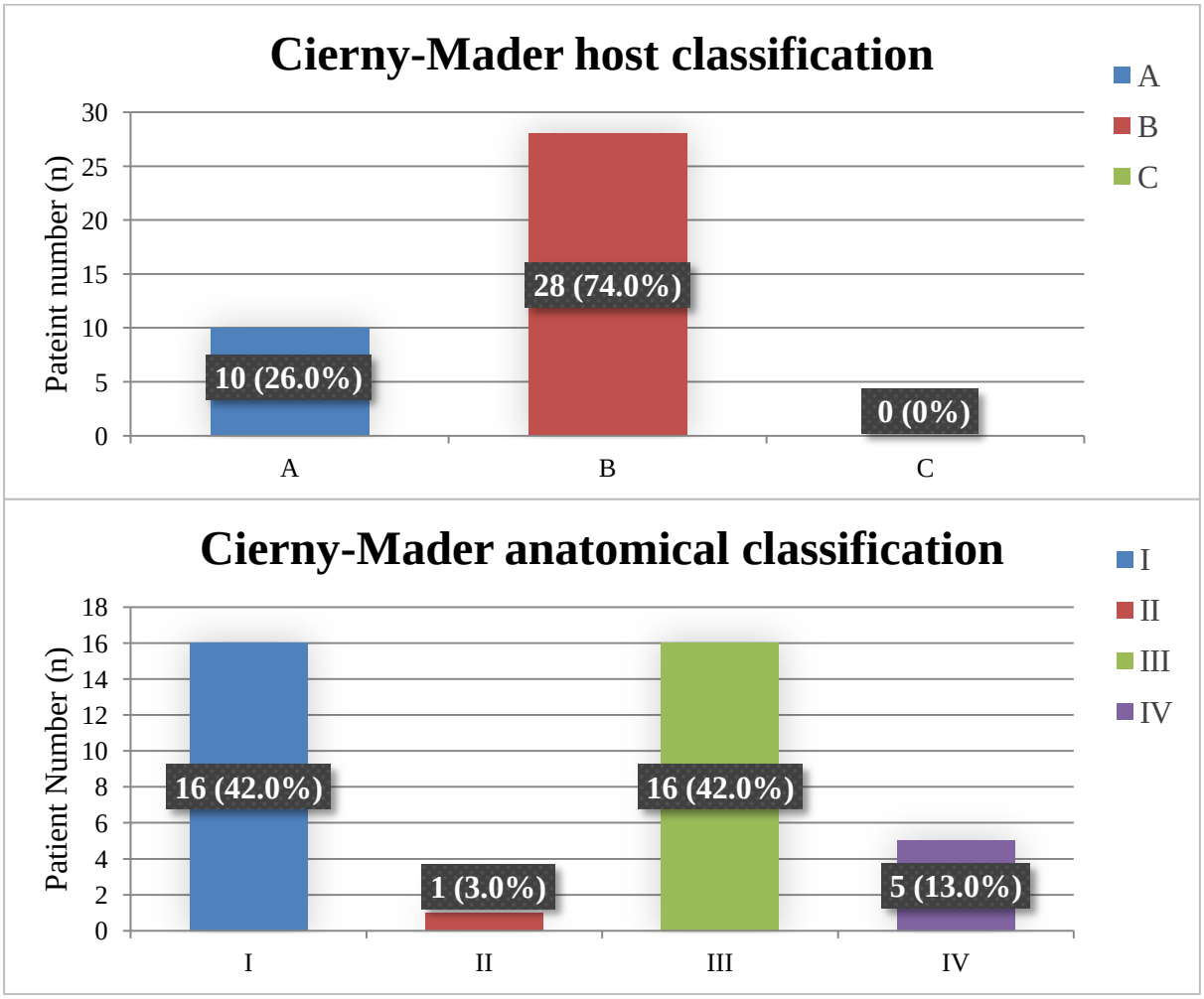

Figure 3.7: Demographics of Cierny-Mader classification in patient group

3.2. Patient demographics and treatment outcome

There was no correlation between these demographics and successful or unsuccessful outcomes from this treatment protocol. This implies that patients' demographics did not influence their outcome with this treatment protocol.

3.3. Microbiology

Table 3.1: Demographics of the various species cultured from bone reamings at initial surgery

Microbiology cultures	**N (%)**
S. aureus	12 (20%)
Methicillin resistant S. aureus	7 (12%)
Pseudomonas	7 (12%)
Klebsiella	5 (8%)
E. faecalis	5 (8%)
Enterobacter sp.	3 (5%)
Proteus species	3 (5%)
E. coli	2 (3%)
Anaerococcus prevotii	2 (3%)
Acinobacter baumani	2 (3%)
Corynebacterium sp.	2 (3%)
No growth	2 (3%)
Coagulase negative Staphylococcus	1 (2%)
Parabacteroides merdae	1 (2%)
Peptostreptococcus anaerobius	1 (2%)
Serratia morcescens	1 (2%)
Citrobacter koseri	1 (2%)
Tuberculosis	1 (2%)

Note: some patients cultured multiple organisms hence the proportion of organisms is larger than the patient sample size.

The above table demonstrates how a wide spectrum of organisms is linked to the causation of chronic osteomyelitis.

3.4. Antibiotic sensitivity

The below table illustrates the various antibiotics required to treat the specified organisms and the graph depicts the drug resistance of the organisms

Table 3.2: Antibiotic sensitivity

Antibiotic Sensitivity	**N (%)**
Cloxacillin	10 (23%)
Vancomycin	10 (23%)
Piperacillin-tazobactam	5 (12%)
Cephalosporins	4 (9%)
Ertapenem	4 (9%)
Meropenem	3 (7%)
Imipenem	2 (5%)
Coamoxiclav	2 (5%)
Linezolid	1 (2%)
Antituberculosis therapy (Isoniazid and Rifampicin sensitive)	1 (2%)

Note: some patients cultured multiple organisms which in the microbiology laboratory could all be sensitive to one antibiotic; hence the patient sample size and number of organisms cultured does not correlate with the figures of antibiotic sensitivity.

When analysing the antibiotics to be given per patient, the drug resistance depicted in Figure 3.8 shows that the standard empiric antibiotics commonly used to treat osteomyelitis would not be adequate. Cloxacillin, suggested by the antibiotic stewardship, would only treat 19% of the causative organisms, 17% of the organisms would be treated by Vancomycin alone, 44% required another agent and 19% required multiple agents for multiple organisms cultured. Importantly, these antibiotics would need to be delivered with a local device and that the elution kinetics of cloxacillin is not known.

Ten percent (10%) of the organisms cultured (n=6) were multidrug resistant MRSA requiring Vancomycin whereas, 2% of the total organisms (n=1) were extensively drug resistant requiring Linezolid (these results are presented based on drug resistance as defined by the

European Centre for Disease Prevention and Control (ECDC) and the United States Centres for Disease Control and Prevention (CDC)) [32].

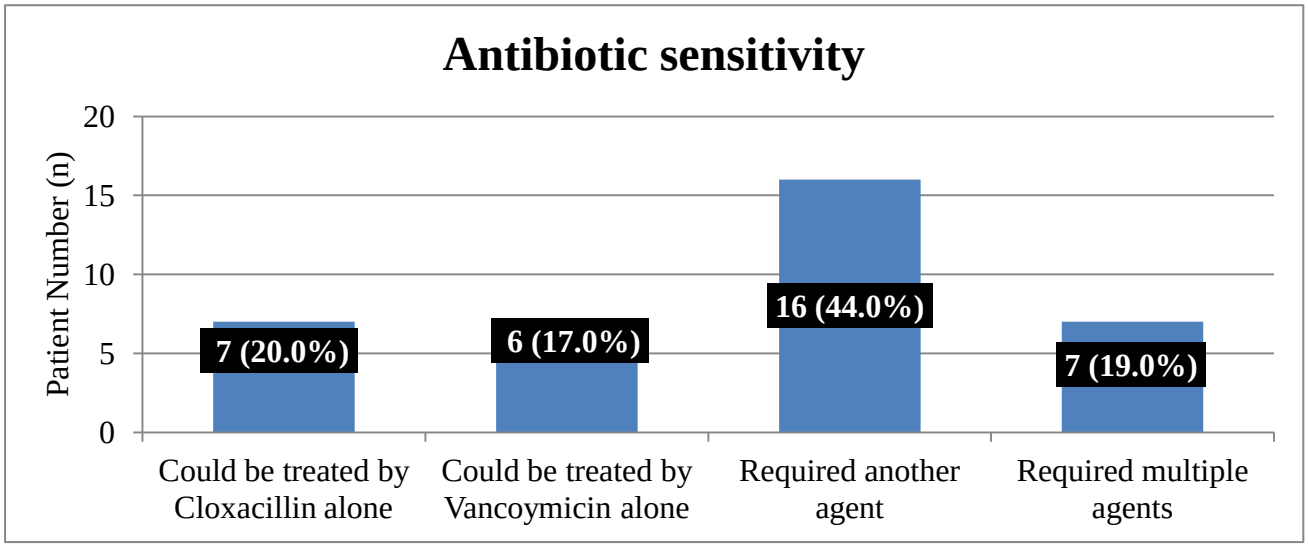

Figure 3.8: Antibiotic sensitivities of specimens

3.5. Microbiological resolution

Of those who were culture positive before treatment (*i.e.* at the initial surgery and DRI), 75.7% were negative post-treatment (at the final surgery) demonstrating the degree of microbiological resolution. This is a conversion rate of 75.67%.

Clinical outcome three months post-treatment

Illustrating the clinical improvement in terms of skin changes and sinus resolution of this intervention at three months follow-up, 84.2% had a good clinical outcome, 10.5% an average clinical outcome and 5.3% a poor outcome (the clinical outcome is graded as defined below).

Table 3.3: Clinical outcomes for patients three months after the treatment

Clinical follow-up outcome	**N (%)**
Good	32 (84.2)
Average	4 (10.5)
Poor	2 (5.3)

Clinical outcome grade:

Good: defined as complete resolution of sinus drainage, wounds, skin changes, pain and function

Average: defined as partial resolution of sinus drainage, wounds, skin changes, pain and function

Poor: defined as incomplete or no resolution of sinus drainage, wounds, skin changes, pain and function

Of the patients who had microbiological resolution (*i.e.* conversion to negative results and cleared sepsis), 89.7% also had a good clinical outcome. Of the patients who had a failed microbiological response, 66.7% still had a good clinical outcome but 11.1% had a poor clinical outcome. Overall, regardless of negative culture conversion, patients had a good clinical outcome (Table 3.4).

Table 3.4: Comparing culture results, after the treatment, to clinical outcomes after three months of follow-up

	Clinical outcome		
	Good	*Average*	*Poor*
Post treatment			
Negative	26 (89.7%)	2 (6.9%)	1 (3.4%)
Positive	6 (66.7%)	2 (22.2%)	1 (11.1%)
Total	32 (84.2%)	4 (10.5%)	2 (5.3%)

3.6. Biochemical markers

When assessing biochemical improvement with the use of inflammatory markers (CRP and ESR) and White Blood Cell counts, there was an overall decreasing trend of septic markers from pre-treatment to post-treatment however, only CRP had a statistically significant decrease as per the *p*-value as shown in Table 3.5.

Table 3.5: Clinical markers before and after the treatment

Chemical marker	**Preoperative (n=38)**	**Post treatment (n=35 for CRP and WCC, n=34 for ESR)**	**p-value***
CRP			
Median (IQR)	17.5 (10-26)	10 (3-18)	0.0043**
White cell counts			
Median (IQR)	19.5 (10-29)	18 (9-27)	0.1983
ESR			
Median (IQR)	16 (8-24)	13.5 (5-20)	0.1116

** Wilcoxon signed-rank test was done to compare median values before and after the intervention and corresponding p-value is presented*

*** Statistically significant ($p < 0.05$)*

Chapter 4: Discussion

The findings obtained from this study were analysed and are reported in reference to other relevant studies. The peculiar findings of the study are highlighted, and the implications of the overall study are discussed. The limitations of the study are described, and recommendations thereof.

4.1. Sample size

Due to the small sample size, our study focused on comparisons before and after treatment to better understand the clinical impact of the treatment. The small sample size also made statistical analysis testing impractical. However, this size is comparable to other studies of its nature in the literature as all the studies of its type had small cohorts.

4.2. Demographics

Although our demographics noted indicated which patient was more likely to suffer from chronic osteomyelitis, there was no correlation between the demographics and successful treatment or unsuccessful treatment. This implies that there is no correlation between those who were more likely to do better with the reviewed treatment protocol and no means to predict outcome based on demographics. HIV was the most commonly occurring co-morbidity amongst the group. This is likely due to the younger age group being mostly affected by HIV, as well as trauma. [32]. In addition, 26% (n=10) of the patients did not know their HIV status or refused testing during treatment. This is a significant proportion when looking at the number of patients who had a positive HIV status (29%, n=17). An interesting correlation could have been made if more of the patients knew their HIV status.

4.3. Antibiotic selection

Antibiotic stewardship suggests the use of Cloxacillin to treat osteomyelitis, which is what primary practitioners would use for such patients. Although current orthopaedic recommendations are that initial empiric antibiotic choice be Vancomycin and Meropenem [12] to cover MRSA and anaerobes, this is not followed in practice in many facilities including at our site due to the traditional use of Vancomycin alone. A patient would also require admission for these intravenous antibiotics which presents its own complexities and is

likely the reason why patients are given long term Cloxacillin, Rifampicin and dressings as a chronic treatment for osteomyelitis.

If patients were treated empirically according to guidelines and given Vancomycin and Meropenem at the outset, this would have covered 30% of the organisms cultured. However, as previously mentioned, systemic antibiotics may not achieve effective local concentrations in damaged tissue especially with a dead space making it inaccessible to systemic antibiotics [16], even though organisms may be susceptible even to empiric antibiotics; the antibiotic effects would be best if delivered locally to the bone.

The literature commonly indicates *S. aureus* as the main organism isolated in all types of osteomyelitis [12]. However, as demonstrated by this study, a wide spectrum of organisms is linked to the causation of chronic osteomyelitis making targeted antibiotic therapy necessary and important once culture results are ascertained.

Of the antibiotics that were sensitive to cultured organisms all, except for Pipericillin-Tazobactam, Sulfamethoxazole and Cloxacillin, have been assessed either *in vitro* or *in vivo* for their elution kinetics and thermostability. All have been found to be thermostable. All have adequate and favourable elution kinetics; including Linezolid [30. Amoxicillin Clavulanate, Ampicillin, Meropenem, Ertapenem and Cephalosporins should be used at a higher dose to extend their elution to a longer time period [15 and 31]. This allows one to use a variety of antibiotics in a cement rod.

4.4 Treatment outcome

This study demonstrated a conversion rate of 75.67% in terms of microbiological response. Of the patients included in the study, 84.2% had a good clinical outcome, and overall a decrease in trend of all septic markers. These results are comparable and on par with the findings reported in other similar study cohorts [7, 15, 21, and 25].

Reily et al. with a sample size of 41 patients and a follow-up of six months found that 76% of infections were cleared, based on clinical examination and serological markers, after the use of antibiotic-impregnated intramedullary nails [21]. Of interest is that Reily et al. found that persistent infections presented within six months after antibiotic nail insertion and postulated that it is possible that the failure of treatment with an antibiotic nail occurs within the first six

months. A repeat follow-up with our cohort could better analyse this finding and be compared.

In a study by Cho et al., the authors had no time frame of follow-up but rather analysed their success based on the negative conversion of their cultures. This group of 40 patients had an 85% success rate [24]. In another study by Sancineto et al., 19 patients were followed-up for 12 months and with a 100% success based on culture conversions to negative results [23].

Most studies poorly explained their basis of a successful outcome thus making our data difficult to compare objectively. There is no score available in the literature for the clinical diagnosis or clinical resolutions of chronic osteomyelitis. Most cohorts simply use observation of a sinus and resolution thereof, pain and stiffness resolution on a subjective scale. In our cohort, skin changes, the presence or resolution of a sinus, patient's opinion on pain function and satisfaction were used. Clinical improvement was graded as poor, average and good but not by any set standard or score as none is available. A set and standard score would allow for a more objective and comparable analysis by researchers and clinicians.

4.5. Patients with poor outcome

Of the two patients who had a poor clinical outcome at three months, both were HIV negative but were smokers. Although the demographics in this study did not correlate with a poorer outcome for smokers, it is known that chronic smoking affects healing [15]. Of these two patients, one had a successful microbiological response with a negative culture conversion and a healed sinus, however due to the initially large wound, the patient required ongoing bone transport and soft tissue coverage. The other patient had sinus resolution and pain resolution however had developed a new separate collection in the leg. This patient had a positive culture post-therapy.

There is no identifiable similarity between patients who had a positive culture post-therapy. They did not culture the same organisms, nor did they have a significant common demographic risk factor. Further follow-up on these patients may provide answers, and possible further DRI and antibiotic cement rod insertion (more than the average amount of three surgeries) could provide evidence regarding the ideal treatment for this group of patients.

4.6. Biochemical markers

Regarding biochemical markers, one can rely on CRP rather than on the WCC or ESR. Although all the markers decreased post-treatment, CRP was the only marker that had a statistically significant decrease.

4.7. Limitations

Limitations of the study include its retrospective nature, the fact that it was non-randomised and that there was no inclusion of a control group. Furthermore, the study sample size was small due to the small amount of patients who underwent the treatment protocol. Ten patients were also excluded from the study due to incomplete records of biochemical markers thus making the sample size smaller. Lastly, due to the Covid-19 pandemic, a two-year follow-up on patients could not be done; however, a longer follow-up period could improve the analysis and assessment of the success rate of the treatment. Although a set treatment protocol was used, some patients required further surgeries for mechanical stability and source control.

4.8. Recommendations for clinical practice

1. Patients with chronic osteomyelitis secondary to an open fracture are offered the set treatment protocol after thorough counselling of the total surgeries and hospital stay involved.
2. Surgeons consider using antibiotic targeted cement rods, cheaply manufactured in a staged surgery method.
3. Patients with chronic osteomyelitis get treated by a team where infectious diseases, microbiologists and surgeons optimise best therapy.
4. Hospitals make provision by providing theatre time and hospital beds for patients with chronic osteomyelitis to be admitted and treated as per the set protocol rather than receiving ineffective long term oral antibiotics and dressings.

4.9. Recommendations for research

Based on the results from this study, the following recommendations are made for future research:

1. Further long-term follow-up to assess if clinical outcome improved with more time for those who had an average outcome with a negative culture result post therapy, as well as to assess long term patient satisfaction and sepsis control.

2. Assessing infection free interval for patients (this would entail a longer follow-up time), as well as a functional scores (e.g. Short Musculoskeletal Functional Assessment).

3. A prospective randomised control trial should be done to compare empiric antibiotic cement rods to targeted antibiotic cement rods, the number of surgeries required in this format and the cost and hospitalisation impacts of the two arms.

4. An objective clinical score for osteomyelitis should be developed and assessed to allow for adequate objective comparison between studies and within studies.

5. A cost analysis should be done to compare this treatment protocol to others to assess if it truly is cost effective.

6. Further systematic review and meta-analyses should be done specifically on antibiotic delivery devices.

Chapter 5: Conclusion

Although chronic osteomyelitis remains a complex disease to treat, the results obtained from this study demonstrate that the use of staged surgery following the use of tailored antibiotic cement rods with debridement, reaming and irrigation had a successful clinical, microbiologic and serological outcome. This treatment protocol is a feasible option for patients with endosteal chronic osteomyelitis secondary to long bone fractures. The reported results are comparable to other similar international studies.

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Appendices

Appendix A: Human Research Ethics Committee (Medical) clearance certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Caterina Nicolaou

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200911 MED20-07-064

NAME: (Principal Investigator)	Dr Caterina Nicolaou
DEPARTMENT:	Orthopaedics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Antibiotic targeted cement rods in Chronic Osteomyelitis, short-term outcomes from a level one South African Trauma Centre
DATE CONSIDERED:	02/10/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Allan Sekeitto, Dr Juan Urrea and Dr Brenda Milner
APPROVED BY:	Dr C Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	28/10/2020

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

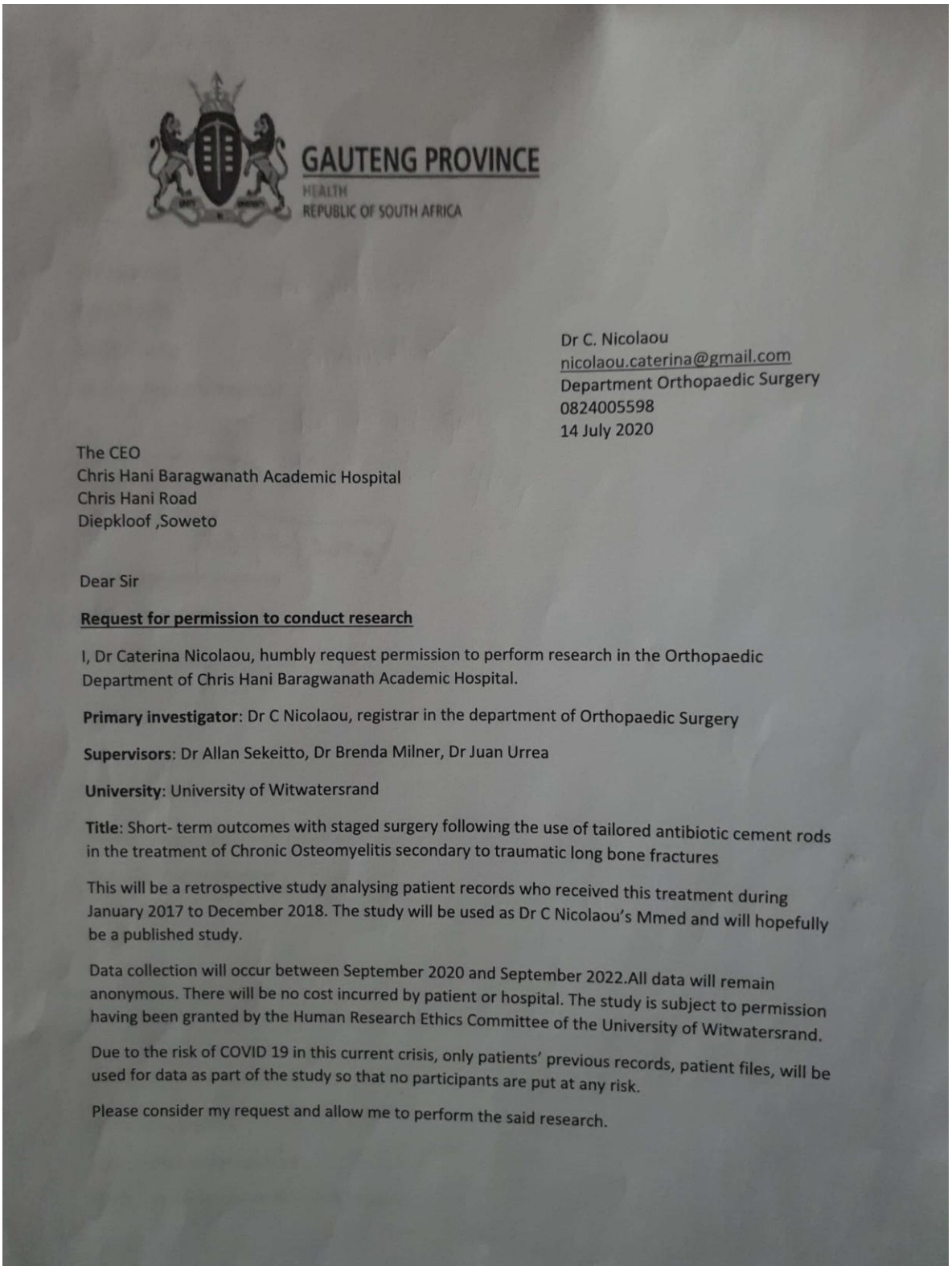
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. 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**. 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 September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

10/11/2020

Appendix B: Hospital CEO permission letter



GAUTENG PROVINCE
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14 July 2020

The CEO
Chris Hani Baragwanath Academic Hospital
Chris Hani Road
Diepkloof ,Soweto

Dear Sir

Request for permission to conduct research

I, Dr Caterina Nicolaou, humbly request permission to perform research in the Orthopaedic Department of Chris Hani Baragwanath Academic Hospital.

Primary investigator: Dr C Nicolaou, registrar in the department of Orthopaedic Surgery

Supervisors: Dr Allan Sekeitto, Dr Brenda Milner, Dr Juan Urrea

University: University of Witwatersrand

Title: Short- term outcomes with staged surgery following the use of tailored antibiotic cement rods in the treatment of Chronic Osteomyelitis secondary to traumatic long bone fractures

This will be a retrospective study analysing patient records who received this treatment during January 2017 to December 2018. The study will be used as Dr C Nicolaou's Mmed and will hopefully be a published study.

Data collection will occur between September 2020 and September 2022.All data will remain anonymous. There will be no cost incurred by patient or hospital. The study is subject to permission having been granted by the Human Research Ethics Committee of the University of Witwatersrand.

Due to the risk of COVID 19 in this current crisis, only patients' previous records, patient files, will be used for data as part of the study so that no participants are put at any risk.

Please consider my request and allow me to perform the said research.

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 3rd August 2020

TITLE OF PROJECT:

Short-term outcomes with staged surgery following the use of tailored anitbiotics cement rods in the treatment of Chronic Osteomyelitis secondary to traumatic long bone fractures.

UNIVERSITY: Witswatersrand

Principal Investigator: Dr C Nicolaou

Department: Orthopaedics

Supervisor : Dr A Sekeitto

Permission Head Department (where research conducted): Yes

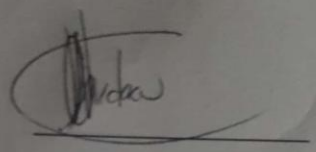
The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects 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: 3/8/2020

Approved/Not Approved
Hospital Management
Date: 25/08/2020

Yours faithfully

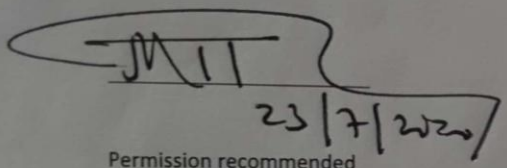


Dr C.Nicolaou

MP0755079

MBBCH Wits

Wits Orthopaedic Registrar



Permission recommended

HOD Orthopaedics

Prof Ramokgopa

Appendix C: Data Collection Sheet

Patient study number	Age	Gender	Initial Diagnosis	Date	Initial Surgery	Septic Diagnosis	Septic Control Surgery	Culture	Culture Result

Appendix D: Demographic characteristics of chronic osteomyelitis patients

Patient characteristics	**N (%)**
Sex	
Male	32 (84%)
Female	6 (16%)
Age	
18 - 30 year olds	9 (24%)
31 - 40 year olds	12 (32%)
41 - 50 year olds	9 (24%)
> 51 year olds	8 (21%)
Comorbidities	
Hypertension	3 (7%)
Tuberculosis and complications thereof	1 (2%)
Chronic Obstructive Pulmonary disease	1 (2%)
Human Immunodeficiency Virus	11 (27%)
Other	2 (5%)
None known	21 (51%)
Diabetes	2 (5%)
HIV	
Positive	11 (29%)
Negative	17 (45%)
Unknown	10 (26%)
Smoking	
Smokers	20 (53%)
Non-Smokers	18 (47%)
Cierny and Mader anatomical classification	
I	16 (42%)
II	1 (3%)
III	16 (42%)
IV	5 (13%)
Cierny and Mader host classification	
A	10 (26%)
B	28 (74%)
C	0 (0%)
Microbiology cultures	
E. coli	2 (3%)
E. faecalis	5 (8%)
S. aureus	12 (20%)
Methicillin resistant S. aureus	7 (12%)
Enterobacter sp.	3 (5%)
Klebsiella	5 (8%)
Pseudomonas	7 (12%)
Corynebacterium sp.	2 (3%)
Fusobacterium nucleatum beta lactam negative	1 (2%)
Anaerococcus prevotii	2 (3%)
Coagulase negative Staphylococcus	1 (2%)
Parabacteroides merdae	1 (2%)
Peptostreptococcus anaerobius	1 (2%)
Acinobacter baumani	2 (3%)
Proteus species	3 (5%)
Serratia morcescens	1 (2%)
Citrobacter koseri	1 (2%)
No growth	2 (3%)
Tuberculosis	1 (2%)

Fracture type	
Open	28 (74%)
Closed	10 (26%)
Antibiotic Sensitivity	
Piperacillin-tazobactam	5 (12%)
Meropenem	3 (7%)
Ertapenem	4 (9%)
Imipenem	2 (5%)
Linezolid	1 (2%)
Cephalosporins	4 (9%)
Cloxacillin	10 (23%)
Ampicillin/amoxicillin	1 (2%)
Coamoxiclav	2 (5%)
Sulfamethoxazole	1 (2%)
Vancomycin	10 (23%)