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# Biodegradable Gentamicin Beads: Finding The Holy Grail For Chronic Orthopaedic Infections

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**Abstract**

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## Introduction

Bacterial infections are one of the most devastating complications in the field of orthopaedic surgery. Especially infections related to implants e.g., cases of infection in total joint arthroplasty (TJA), or infections related orthopaedic traumatology where implants are used for bone fixation are burdensome and difficult to treat. The infection rates vary based on the etiology of the infections. In cases of prosthetic joint infections (PJI) the infection rates vary from <1% in primary total hip arthroplasty up to 10 to 14% in spine surgery or revision arthroplasty. In the specific case of orthopaedic traumatology, the chronic osteomyelitis rates are even up to 50% according to studies regarding surgical fixation of open fractures.

Existing treatment strategies include the use of antibiotic-loaded polymethyl methacrylate (PMMA) cement spacers or beads to elevate local antibiotic levels at the surgical site.

Studies have demonstrated a significant reduction in infection rates using antibiotic- impregnated cement in total hip arthroplasty and total knee arthroplasty patient populations. Conversely, other studies indicated limited clinical benefit, albeit with various antibiotics and concentrations and poor descriptions of elution kinetics. Additionally, once the antibiotics have eluted from a non-absorbable cement, the surface becomes a foreign body that is subject to bacterial colonisation and biofilm formation.

**Aim:** To study the outcome of orthopaedic infections treated by antibiotic beads and cement.

**Objective:** To study the effectiveness of antibiotic beads in treatment of orthopaedic infections and the complications, if any.

## Materials And Methods

**Study Design:** Prospective study.

**Study Duration:** 20 various cases of Orthopaedics related infections consenting for use of antibiotic loaded cement from January 2021 to December 2021.

**Study Setting: This** study will be conducted at Mahatma Gandhi Mission Medical College, Navi Mumbai, for patients diagnosed with orthopaedics related infections, diagnosed on the basis of history, clinical findings and laboratory investigations, consenting for treatment with antibiotic cement, after failure of conservative treatment for at least 2 weeks.

**Sample Size:** 20 Patients.

**Study Population** Inclusion criteria

1. Chronic osteomyelitis
2. Prosthetic joint infections

3. Chronic orthopaedic infections in diabetics
4. Infected fractures Exclusion criteria
1. Infections associated with compartment syndrome
2. Patients with co-morbid conditions and not fit for procedure
3. Isolated fractures with neurovascular injuries
4. Patient not consenting for treatment

**Data Assessment**: All patients will be evaluated using the following parameters –

a. ASEPSIS scoring system
b. Lab investigations – ESR, CRP
c. Culture and sensitivity reports

**Post Operative Protocol**: Serial ASEPSIS score and ESR and CRP will be checked at preoperatively and thereafter postoperatively at 1 month, 2 month, 4 month, 6 month to assess recovery from the infection.

**ESR & CRP**

| Laboratory parameters | Normal / (-) | Increased/ (+) |
|---|---|---|
| **CRP** | <6 mg/dl | >6 mg/dl |
| **ESR** | <15 mm/hr | >15 mm/hr |

Preparation of Beads

1) Mixing of powder with antibiotic solution/powder in the appropriate amount.
2) Mix for appropriate time.
3) Application of antibiotic paste over the mould of appropriate size for the appropriate setting time.
4) Separation of beads from the mould.
5) Insertion of beads



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ASEPSIS SCORE

| **Wound Characteristics** | **Proportion Of Wound Affected** | | | | | |
|---|---|---|---|---|---|---|
| | 0 | <20 | 20-39 | 40-59 | 60-79 | >80 |
| Serous Exudate | 0 | 1 | 2 | 3 | 4 | 5 |
| Erythema | 0 | 1 | 2 | 3 | 4 | 5 |
| Purulent Exudates | 0 | 2 | 4 | 6 | 8 | 10 |
| Seperation Of Deep Tissues | 0 | 2 | 4 | 6 | 8 | 10 |
| **Criteria** | | **Points** | | | | |
| Proportion Of Wound Affected Antibiotics | | 10 | | | | |
| Drainage Of Pus Under La | | 5 | | | | |
| Debridement Of Wound Under Ga | | 10 | | | | |
| Serous Discharge* | | Daily 0-5 | | | | |
| Erythema* | | Daily 0-5 | | | | |
| Purulent Exudate* | | Daily 0-10 | | | | |
| Seperation Of Deep Tissue* | | Daily 0-10 | | | | |
| **Isolation Of Bacteria** | | **10** | | | | |
| **Stay As Ip For >14 Days** | | 5 | | | | |

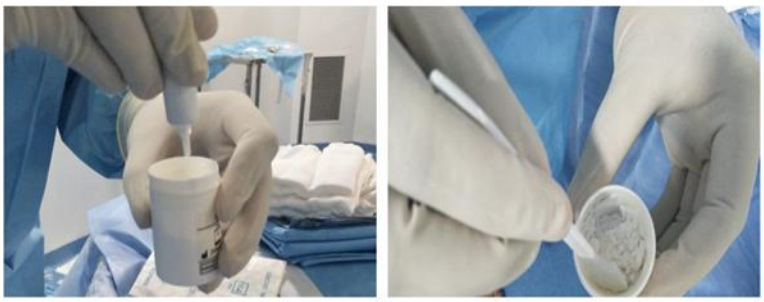

**FIGURE 2: MIXING OF THE ANTIBIOTIC BEAD**



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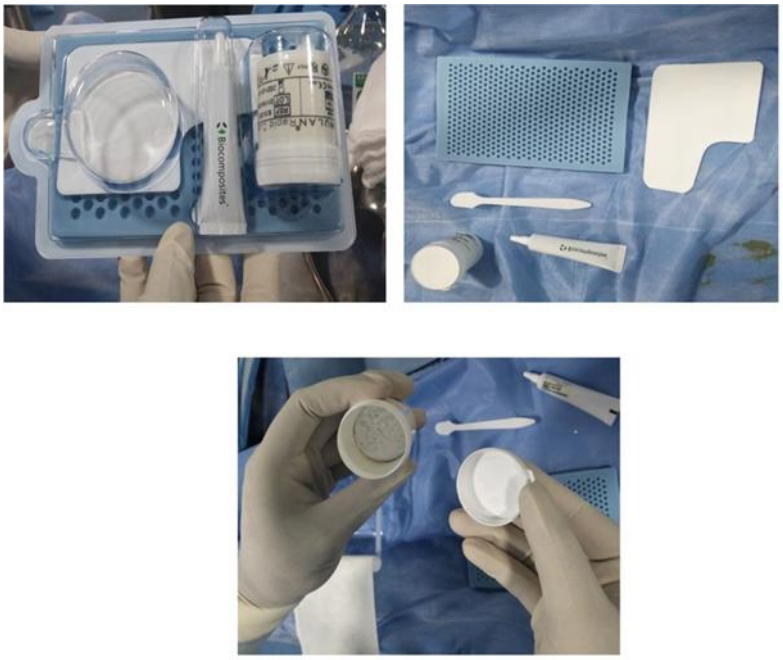

FIGURE 1: ANTIBIOTIC BEAD KIT WITH ANTIBIOTIC POWDER

FIGURE 3: SETTING AND SEPERATION OF ANTIBIOTIC BEADS

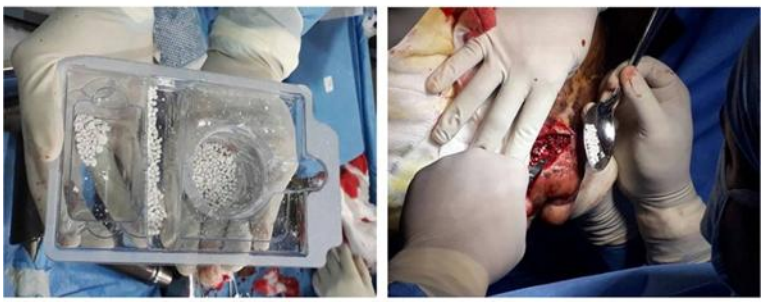

FIGURE 4: APPLICATION OF ANTIBIOTIC BEADS

## Observation And Results



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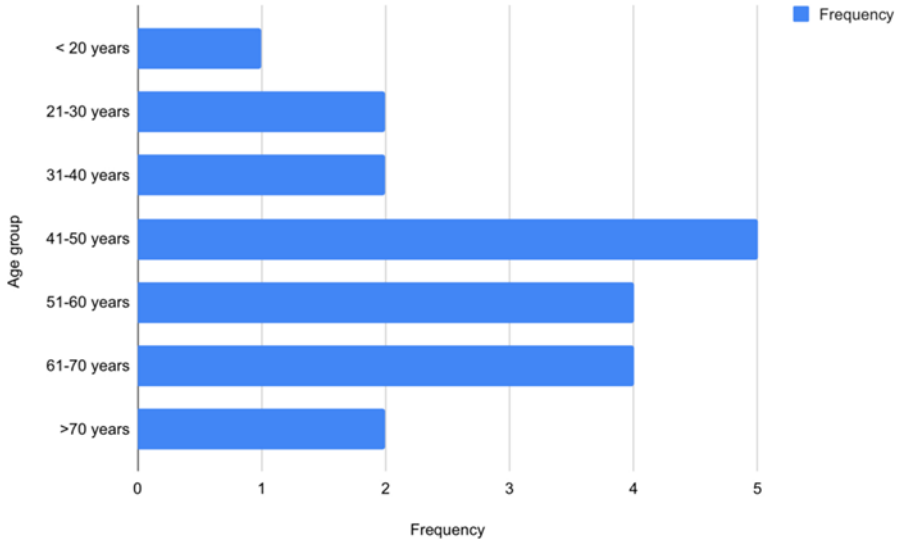
**TABLE: Distribution of the subjects in the study based on the age**

| Age range in years | Frequency | Percentage |
|---|---|---|
| < 20 years | 1 | 5 |
| 21-30 years | 2 | 10 |
| 31-40 years | 2 | 10 |
| 41-50 years | 5 | 25 |
| 51-60 years | 4 | 20 |
| 61-70 years | 4 | 20 |
| >70 years | 2 | 10 |
| **Total** | 20 | 100 |

**GRAPH: Distribution of the subjects in the study based on the age**




Average age of participants = 49.25

**TABLE: Distribution of subjects in the study based on the gender**

| Gender | Frequency | Percentage |
|---|---|---|
| Male | 16 | 80 |
| Female | 4 | 20 |
| Total | 20 | 100 |



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**GRAPH: DIistribution of subjects in the study based on the gender**

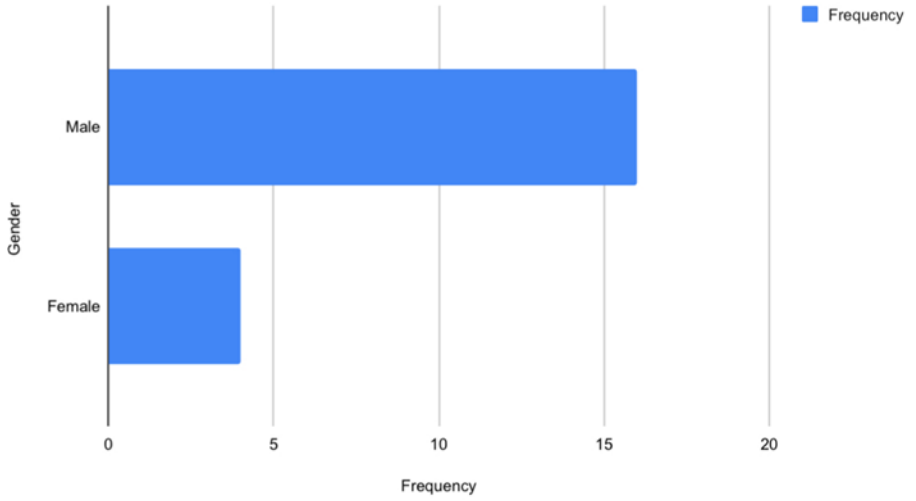


**TABLE: Distribution of subjects in the study based on the diagnosis**

| Diagnosis | Frequency | Percentage |
|---|---|---|
| Chronic Osteomyelitis | 4 | 20 |
| Prosthetic infections | 16 | 80 |
| Total | 20 | 100 |

**GRAPH: Distribution of subjects in the study based on the diagnosis**

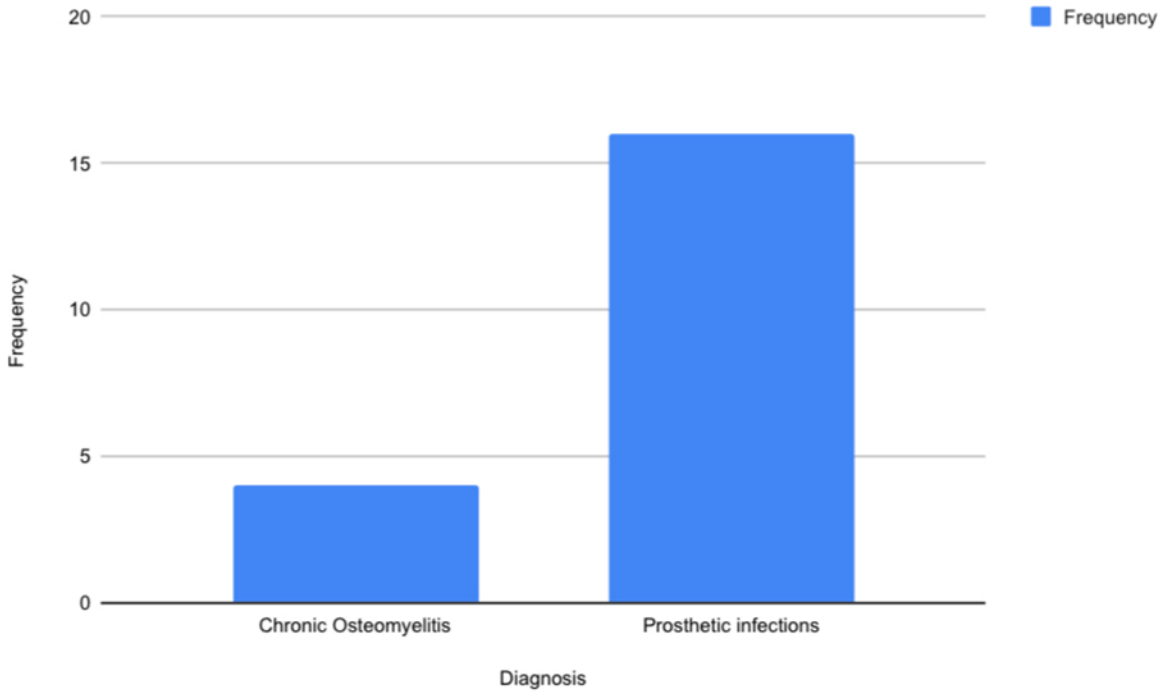




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**TABLE: Distribution of subjects in the study based on the CRP at various time intervals**

| CRP | Preop | 1m | 2m | 4m | 6m |
|---|---|---|---|---|---|
| <6 mg/dl | 0 | 0 | 1 | 2 | 4 |
| >6 mg/dl | 20 | 20 | 19 | 18 | 16 |
| Total | 20 | 20 | 20 | 20 | 20 |

**GRAPH: Distribution of subjects in the study based on the CRP at various time intervals**

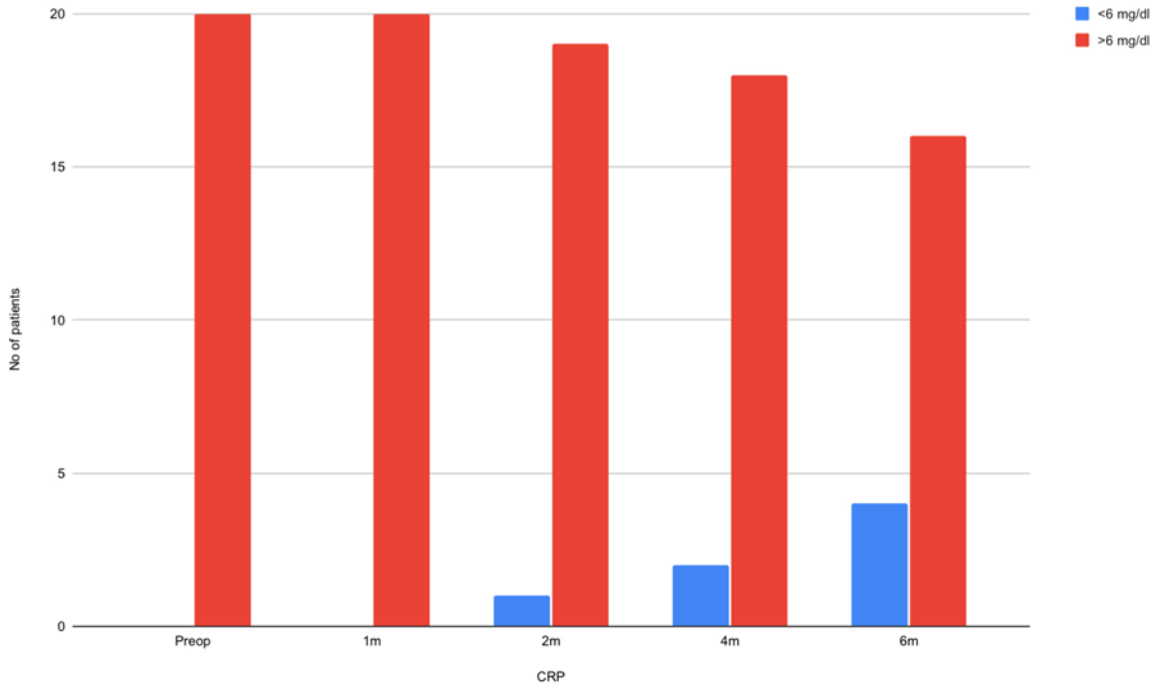


**TABLE: Distribution of subjects in the study based on the ESR**

| ESR | Preop | 1m | 2m | 4m | 6m |
|---|---|---|---|---|---|
| <15 mg/dl | 0 | 0 | 1 | 1 | 2 |
| >15 mg/dl | 20 | 20 | 19 | 19 | 18 |
| Total | 20 | 20 | 20 | 20 | 20 |



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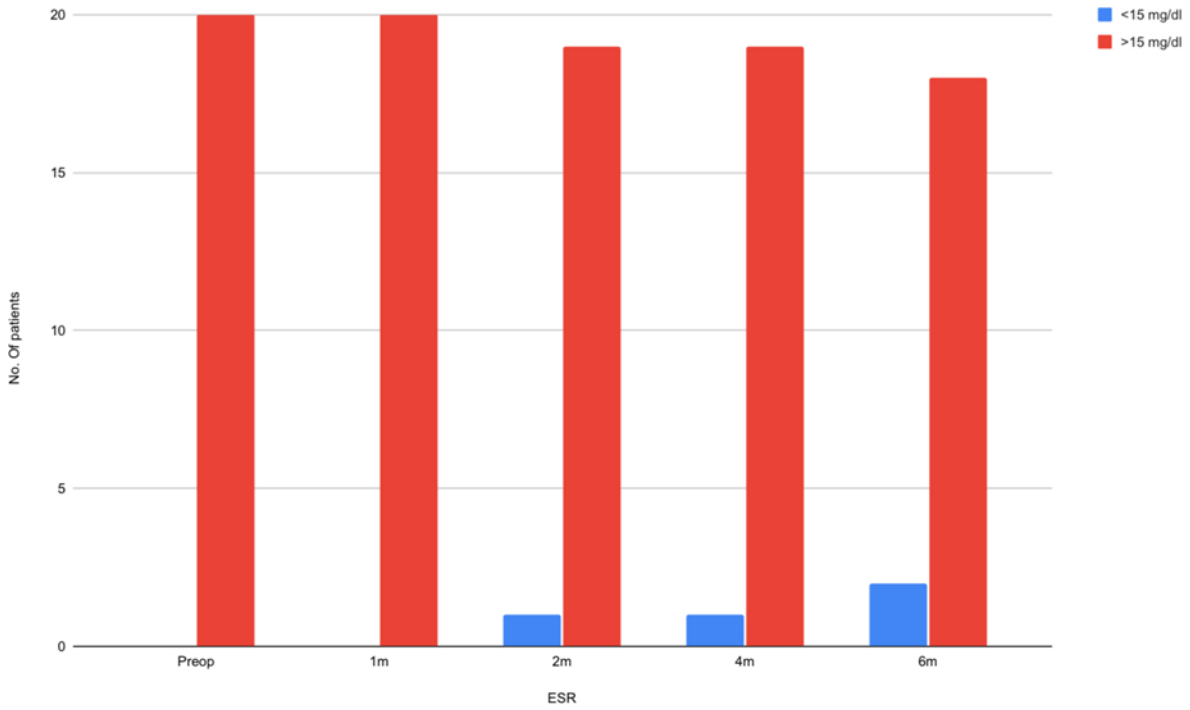
**GRAPH: Distribution of subjects in the study based on the ESR**




Mean preoperative ESR = 59 Mean postoperative ESR = 32.51

**TABLE: Distribution of subjects based on the culture report at various time intervals**

| | Preop | 1m | 2m | 4m | 6m |
|---|---|---|---|---|---|
| Postive | 20 | 18 | 17 | 15 | 10 |
| Negative | 0 | 2 | 3 | 5 | 10 |
| Total | 20 | 20 | 20 | 20 | 20 |

**GRAPH: Distribution of subjects based on the culture report at various time intervals**

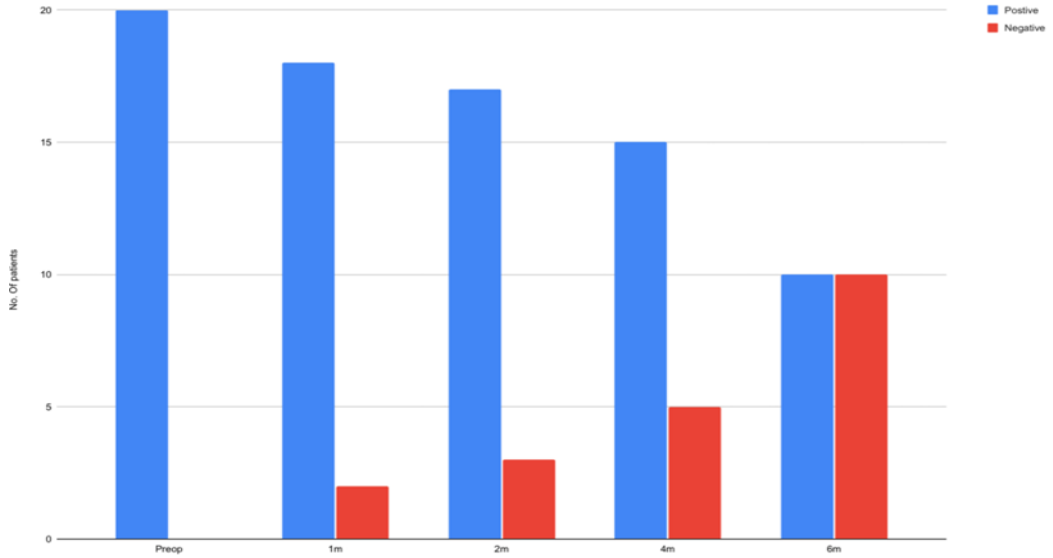





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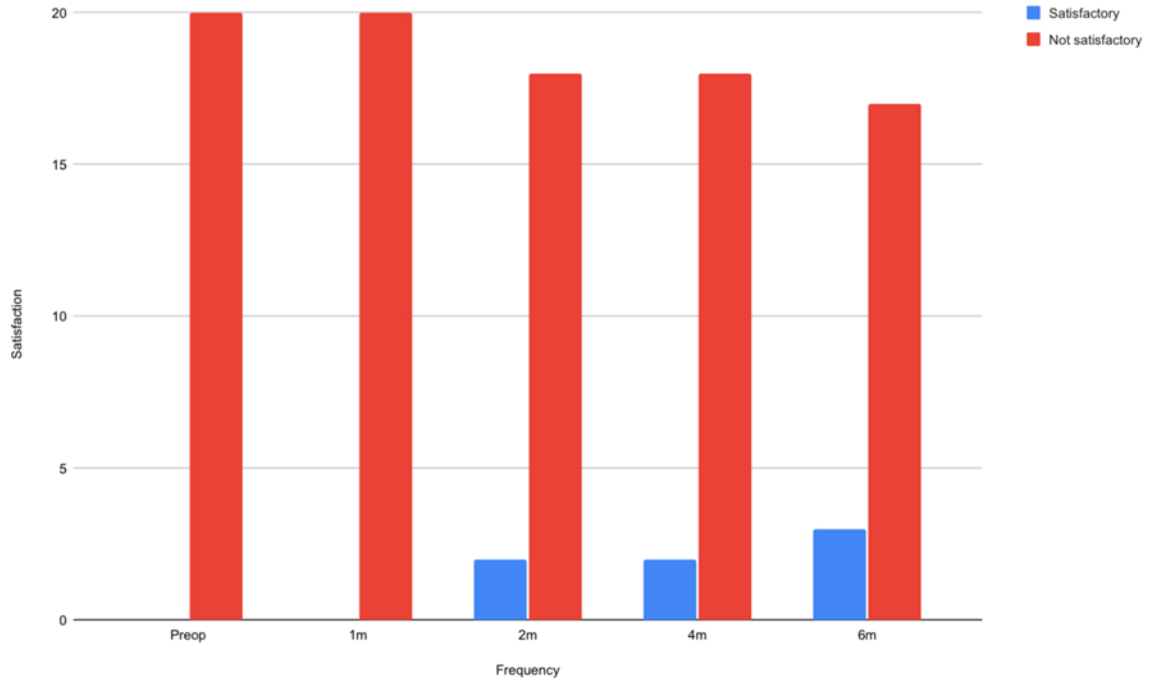
**TABLE: Distribution of subjects in the study based on the clinical satisfaction ASEPSIS Score**

| Clinical satisfaction | Preop | 1m | 2m | 4m | 6m |
|---|---|---|---|---|---|
| Satisfactory | 0 | 0 | 2 | 2 | 3 |
| Not satisfactory | 20 | 20 | 18 | 18 | 17 |
| Total | 20 | 20 | 20 | 20 | 20 |

**GRAPH: Distribution of subjects in the study based on the clinical satisfaction ASEPSIS Score**




## Discussion

Bone and joint infections pose a formidable challenge to the orthopaedic surgeon. The high success rate obtained with antibiotic therapy in most bacterial diseases has not been obtained in bone and joint infections because of the physiologic and anatomic characteristics of bone. The overall surgical site infection rate has been estimated by the U.S. Centre for Disease Control and Prevention (CDC) to be 2.8% in the United States.

Approximately 300,000 surgical site infections occur each year in the United States. Although bacteraemia is common (estimated to occur 25% of the time after simple tooth brushings), other etiologic factors must be present for an infection to occur. The mere presence of bacteria in bone whether from bacteraemia or from direct inoculation is insufficient to produce osteomyelitis. Illness, malnutrition, and inadequacy of the immune system also can contribute to bone and joint infections. As in other parts of the body, bones and joints produce inflammatory and immune responses to infection. Osteomyelitis occurs when an adequate number of a sufficiently virulent organism overcomes the host's natural defences (inflammatory and immune responses) and establishes a focus of infection. Local skeletal factors also play a role in the development of infection. For example, the relative absence of phagocytic cells in the metaphyses of bones in children may explain why acute hematogenous osteomyelitis is more common in this location. The peculiarity of an abscess in bone is that it is contained within a firm structure with little chance of tissue expansion. As infection progresses, purulent material works its way through the Haversian system and Volkmann canals and lifts



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the periosteum off the surface of bone. The combination of pus in the medullary cavity and in the subperiosteal space causes necrosis of cortical bone. This necrotic cortical bone, known as a sequestrum, can continue to harbor bacteria despite antibiotic treatment. Antibiotics and inflammatory cells cannot adequately access this avascular area, resulting in failure of medical treatment of osteomyelitis. Recognising these unique characteristics of bone infections, the best course is prevention. The orthopaedic surgeon should evaluate the risk of infection in each patient by considering patient-dependent and surgeon-dependent factors. Patient-dependent factors include nutrition, immunologic status, and infection at a remote site. Surgeon-dependent factors include prophylactic antibiotics, skin and wound care, operating environment, surgical technique, and treatment of impending infections, such as in open fractures. Simply stated, it is much easier to prevent an infection than it is to treat it.

The number of orthopaedic implant surgeries is rising in the past years and is expected to increase in the upcoming years. Not solely the absolute numbers of PJIs are increasing, but also the relative infection rates are increasing. These numbers are rising due to the aging population and a higher demand for joint replacements due to higher activity levels of these patients. Due to these facts, the average patient undergoing TJA has more comorbidities resulting in a higher risk of infection. Treatment of orthopaedic infections as PJIs and chronic osteomyelitis are difficult, invasive, expensive, and they cause a significant increase of morbidity and even mortality.

Periprosthetic infection (PI) is a serious complication of total joint arthroplasty with high rates of associated morbidity, and a growing body of data suggests that bacterial biofilms are the underlying cause. Within a biofilm, bacteria display a 1,000-fold tolerance to antibiotics than their planktonic counterparts and significant resistance to innate and adaptive host immunity. Moreover, biofilms associated with orthopaedic hardware are typically difficult to culture using conventional clinical microbiological methods, and the lack of a definitive diagnosis may result in an underestimate of infection rates. Consequently, the underlying infection is difficult to diagnose and treat, and often the only effective intervention is the twin strategy of thorough debridement and prostheses removal.

Treatment of an orthopaedic infection may require antimicrobial and surgical treatment. Antibiotic treatment alone may be sufficient, but several principles should be followed. The organism should be accurately identified, and its antimicrobial susceptibility should be determined. The correct antibiotic, preferably bactericidal, should be chosen based on the MIC and SBC. The antibiotic must be delivered to the organism in sufficient concentration to destroy it. Surgery may go hand in hand with antibiotic treatment. Surgery can accomplish in 1 hour what the body and antibiotic treatment may require days or weeks to do. The purpose of surgery is augmentation of the host response. Debridement reduces the inoculum and removes necrotic and avascular bone, bacteria, and harmful bacterial products. Surgery is not always necessary, but it is essential when pus is found on aspiration or when radiographic changes of osteomyelitis are seen, indicating pus, necrotic material, and chronic inflammation. If these are not present, a trial of antibiotic treatment is appropriate only after culture material has been obtained. If the patient does not respond to antibiotic treatment in 36 to 48 hours, the wrong antibiotic has been chosen or an abscess has formed. After 48 hours, the sensitivity should have been reported, and a correct organism specific antibiotic can be chosen. If an abscess has formed, surgery is indicated.

Several routes of antibiotic treatment exist. Oral antibiotics are still the most commonly used. Intravenous application may be required for more serious infections that do not respond to oral antibiotics. Local delivery of antibiotics also can be beneficial. Polymethyl methacrylate (PMMA) beads impregnated with heat-stable antibiotics (tobramycin, vancomycin, and gentamicin) have been used since the early 1970s. An additional method of local antibiotic delivery is that of mixing autogenous iliac crest bone graft with piperacillin or vancomycin. Antibiotics must be chosen carefully.

Treatment of PJIs or chronic osteomyelitis differs based on their etiology, but the common denominator for treatment is multimodal; containing surgical debridement, systemic antibiotic treatment and local antibiotic treatment. PJIs can be treated by debridement surgery, antibiotics, irrigation and implant retention (DAIR), a one stage replacement surgery, or a two stage replacement surgery



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depending on the duration of infection, the type of causative pathogen, status of soft tissues and the health status of the patient. Chronic osteomyelitis can be treated in a one-stage or two-stage surgery as well and the choice of treatment is based on the same conditions. Two-stage surgeries are required in delayed infections, severe infections with systemic symptoms, infections with pathogens that are difficult to treat, and cases of infection with compromised soft tissues. The first stage of this treatment algorithm consists of implant or hardware removal, debridement surgery and implantation of a local antibiotic carrier. During the second stage, the local antibiotic carrier is removed. Subsequently, in the case of PJIs, a new endoprosthesis is implanted, where in the case of chronic osteomyelitis the bone defect is filled with either allograft, autograft or a bone void filling biomaterial.

Bone cement is used for almost 150 years since Gluck introduced it in 1870 for fixation of a total knee prosthesis. Back then the bone cement consisted mainly of plaster and colophony, but since the introduction of this bone cement many researchers were looking for an optimization for fixing implants to bone. In 1960, Sir John Charnley introduced PMMA as a new type of bone cement for fixation of the total hip prosthesis in total hip replacement surgery and since this introduction, PMMA is used as golden standard in fixation of cemented total joint arthroplasty. Only a few years after PMMA was introduced, Buchholz and Engelbrecht introduced the concept of combining PMMA and antibiotics in order to achieve a high local antibiotic concentration in treatment of bone infection. With his research, Buchholz showed that PMMA bone cement was capable of releasing different materials or substances like antibiotics and copper ions from its surface. At first, antibiotic loaded PMMA was used to prevent from bacterial infections, but in 1972, Buchholz introduced this principle as a treatment strategy for PJIs. In the past decades, the optimization of antibiotic-loaded PMMA became an important research topic in the improvement of prophylaxis and treatment of PJIs. PMMA is fabricated by mixing a polymer powder with a monomer liquid resulting in an exothermic polymerization reaction leading to a solid rigid material. Antibiotics and other substances are added to PMMA by admixing them to the polymer powder before adding the monomer. As a result, the antibiotics are incorporated between the PMMA chains during the polymerization process. Antibiotic release after incorporation is based on reciprocal diffusion and is divided into two different phases. The initial release of antibiotics, called burst release, is a quick response after implantation resulting in an early (minutes to hours) high local concentration of antibiotics. This burst release is a surface phenomenon where the antibiotics of the surface dissolute into the body fluids out of the PMMA. The second phase, called sustained release, follows after several days and results in a significantly lower, but prolonged local antibiotic concentration. Sustained release is a phenomenon where water-soluble antibiotics diffuse out of the PMMA after depth penetration of the water containing body fluids; because PMMA is hydrophilic it will attract water molecules resulting in a release of the water- soluble antibiotics into the body fluids. Different in vitro studies showed that the pharmacokinetic release profiles of PMMA can be optimised by adjusting several properties of the PMMA. Since antibiotics are released by dissolution after contact with body fluids, an increase of the surface roughness and the porosity of the PMMA result in an increase of surface area, leading to an increased antibiotic release. The increase of porosity of PMMA can be easily achieved by hand mixing the PMMA instead of vacuum mixing. Another possibility to increase the release capacities of the PMMA is to increase the dissolution capacity by adding polymeric fillers (e.g., xylitol and glycine) and using highly water-soluble substances.

It is important to select the type of antibiotics with caution, since not all types of antibiotics are suitable for incorporation in PMMA. Because antibiotics are incorporated between the PMMA chains, it is important to realize that different types of antibiotics can have different effects on the PMMA. Some antibiotics can influence the orientation and the cross-linking of the polymer chains resulting in changes in the viscosity after mixing, the polymerization time, concentration of incorporated antibiotics, and the mechanical strength and stiffness or of the PMMA. In addition to the effects of antibiotics on PMMA, PMMA can influence the effectiveness of antibiotics as well. Antibiotics have to be heat stable due to the exothermic polymerization reaction; antibiotics must be water soluble for dissolution out of the PMMA



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and the must be available in powder form for admixing them into the polymer powder.

Besides, these physicochemical material properties the antibacterial properties are of great importance for treatment of orthopaedic infections. Ideally, the selected antibiotics should be bactericidal, should be broad-spectrum and they should have a low risk of resistance induction, hypersensitivity and/or allergies. Antibiotics often used in clinical practice are gentamycin and vancomycin in Europe, and Tobramycin in the United States. Depending on the clinical situation, it is also possible to add multiple antibiotics to PMMA instead of adding one single type of antibiotics. These so-called, double-antibiotic bone cements are often used in cases of septic revision arthroplasty after PJIs for implant fixation. The rationale for using PMMA bone cements with two different types of antibiotics is based on the broadening of the antibiotic spectrum, but is also based on the synergistic effects of some combinations of antibiotics. The synergistic effects of the combination of these antibiotics cause a mutual increase of antibiotic release but can also increase the mutual antibacterial efficacy. Heat-stable antibiotics are required for PMMA applications; quinolones have shown detrimental effects on chondrocytes and fracture healing; and tobramycin at intermediate levels of concentration (400 µg/mL) can decrease cell replication. In general, vancomycin is less toxic to osteoblasts at high local concentrations than other aminoglycosides and rifampin and the quinolones should not be administered when bone regeneration is an issue.

A 2 to 3 cm area around each bead has a high concentration of antibiotic. With tobramycin and vancomycin, the peak concentration of antibiotic delivered to local tissue occurs on the first day and lasts for only approximately 1 week. This local delivery system avoids systemic toxicity; however, it requires removal (usually surgical) within 4 weeks.

A more attractive biodegradable system is the collagen-gentamicin sponge, which obviates the need for surgical removal and delivers higher concentrations of antibiotics than PMMA beads. It has been suggested that antibiotic release by this method may be complete within 4 days.

Lactic acid polymerase may be the next step in local biodegradable antibiotic delivery systems. This system delivers a high concentration of quinolines (bactericidals for probable pathogens of chronic osteomyelitis) for 60 days, with a peak release of antibiotics at day 15.

## Conclusion

Local application of biodegradable antibiotic beads has better outcome for controlling chronic orthopaedic infections with adjunct systemic antibiotics than systemic antibiotics alone.

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