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# THE CURRENT TREND IN TREATMENT FOR OSTEOMYELITIS

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**ABSTRACT:** Osteomyelitis is a very serious disease caused by bacteria, especially *Staphylococcus aureus*, which directly attacks the bones tissues. Many physicians and surgeons are still looking for the basic cure of the disease. This article mainly focuses on the different kinds of treatments using new drug formulations. Vancomycin coated with chitosan polymers, biodegradable scaffolds, use of major limb amputations with a modified Lautenbach technique, and use of telavancin drug for outpatients is currently used for the treatment of osteomyelitis. Osteomyelitis is classified based on the cause of the disease and also the treatment. Many research works have been carried out which gives us prospects for the treatment of the disease. The pros and cons associated with different methods used for the treatment of the disease are discussed. These methods give us a better idea about the treatment of the disease and also helps in restricting the disease without causing larger damage. The usage of PMMA beads has shown better results for the treatment of Chronic Osteomyelitis.

## INTRODUCTION:

**1.1 Definition:** Osteomyelitis is a disease that causes progressive inflammation to the bone and bone marrow. It also affects the facial skeleton in the mucosal area [1]. The disease causes inflammation, which leads to certain occurrences such as contiguous infection, direct inoculation, or spreading of microorganisms due to sanctification, affecting bone [2].

**1.2 Classification:** The disease is classified by different authors, but the classification systems by Waldvogel [3] and Cierny [4] is widely followed as per the medical literature and also in the clinical practices.

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Under the Waldvogel system, it is classified based on the following

- Duration of the disease in the area, *e.g.*, Acute Osteomyelitis or Chronic Osteomyelitis.
- Origin of the infection, such as hematopoiesis, when it originates from a bacteria or as a contiguous, which focuses on the infection originates from the nearby tissue.
- Finally, it is classified as vascular insufficiency.

According to Waldvogel classification, the disease is not caused due to direct invasion of the microorganisms to the site of the bone after trauma or surgery. The system is known to be etiologic classification as it acts only as a guideline for any surgical or antibiotic therapy. The system is said to have few values in clinical practice based on described pathogenesis of the disease. Cierny-Mader classification is a type of clinical classification which is based on features such as

anatomic, clinical, and radiological. It classifies osteomyelitis into four types based on the anatomical stages.

Stage 1, also known as Medullary osteomyelitis, in which osteomyelitis can only occur in the area of the medullary cavity of the bone.

Stage 2, also known as Superficial osteomyelitis, where the disease is said to cause infection to the cortical bone and most often occurs due to direct inoculation or a contiguous focus infection.

Stage 3, also known as Localized Osteomyelitis, in which the disease causes infection to both cortical and medullary bone. Here, the stability of the bone can be seen and the bone diameter is not being entirely affected by the infection.

Stage 4, also known as Diffuse osteomyelitis, in which the disease is said to cause infection to the entire bone affecting its thickness and stability.

**1.3 Causes for Osteomyelitis:** Among various types of osteomyelitis, Chronic osteomyelitis is one with a high rate of relapse in spite of successful treatment. Relapses are the procedures which will guide the clinical pharmacist to use prolonged and multiple antibiotic treatments [5-6], which may increase the spreading of multi-drug-resistant (MDR) bacteria, such as gram-negative bacterias [7-8]. Prolonged treatment will also give side effects such as ototoxicity and nephrotoxicity of aminoglycosides [9].

Pyogenic bacteria are the major cause of the development of osteomyelitis, along with mycobacteria and fungi. Inflammation and subsequent bone damage are the major effects to be considered along with the spreading of bacterial infection to the soft tissues [10]. The disease is majorly caused by infection due to microorganisms such as *Staphylococcus aureus* [14]. *Staphylococcus aureus* bacteria such as methicillin-sensitive aureus (MSSA) and methicillin-resistant aureus (MRSA), are the most common cause of acute hematogenous osteomyelitis (AHO) in children worldwide [11, 12, 13]. The report states that there are more than 85% hematopoiesis or acute osteomyelitis cases in children below the age group 17 [24]. In recent years, Community-Associated MRSA is reported as the most spreading disease in pediatric patients [29].

It causes several other diseases also due to its tendency to produce cytotoxin such as, Panton-Valentine leukocidin (PVL), and also some other toxins which are linked with *S. aureus*, such as enterotoxin B and phenol soluble modulins [29-32]. Toxin production tends to give certain complications such as abscess development, thrombosis in the veins, and sepsis [29, 32-34]. The antibiotic drugs that are used for the treatment of MRSA are different from those used in the treatment of AHO as it is the majority caused by *Streptococcus pyrogens* and MSSA.

**2. Types of Osteomyelitis:** Chronic osteomyelitis is an example of Osteonecrosis, which develops due to improper treatment of the bone in the acute phase [25]. This disease can also be related to local osteoporosis, which is caused by bone resorption due to secretions of various microbes and presence of certain bacterias such as *Staphylococcus aureus* followed by *P. aeruginosa*, β-hemolytic streptococci, Salmonella species, and *E. coli* [26]. Chronic osteomyelitis occurs due to the coexistence of infected, nonviable tissues and an ineffective host response [63].

Acute osteomyelitis is a big problem in society and its very hard to find the cure, following edema, congestion in the vascular system, and all thrombosis. In the initial stage of the diseases, there is a decrease in the vascular supply to the bone as a result of an infection in the soft tissue. Formation of dead tissue in the bone may occur in a large way due to obstruction of supply to the medullary and periosteal blood in the body [62]. The disease can be restricted from spreading with aggressive antibiotic therapies.

Primary epiphyseal osteomyelitis is a rare disease caused by mycobacteria [21]. Certain Species of Mycobacterium acts as a pathogen for the cause of primary epiphyseal osteomyelitis disease, mostly in the pediatric patients and in infants, who are already a subject for the vaccination against Mycobacterium bovis Bacille Calmette-Guérin (BCG) or pulmonary tuberculosis and also when, the symptoms gives no response to the antibiotic treatments [21]. BCG osteomyelitis is an unusual occurrence caused due to the vaccination process of BCG in a normal patient with normal immune response and also occurs in healthy children [21, 22].

Diagnosis and the treatment of the disease caused by Mycobacterium species are very difficult [21]. Difficulty in the treatment may occur when the area of abrasion is being restricted to the joints of the bone (which doesn't vascularise easily), the slow response to the chemotherapy treatment, and improper removal of the abrasion area [21]. For all these reasons, the disease may occur repeatedly and require operation several times [21-23]. The removal of the area of the abrasion is very important, as well as challenging to stop the disease reoccurrence.

Native vertebral osteomyelitis (NVO) is a very rare disease without any age limit for its occurrence [15]. Many incidences of NVO is seen in the patients of 70 years and older [17]. For this matter, the cases of the patient with higher age having NVO are increasing. This infection commonly shows different characteristics in patients with higher age [18, 19].

Emphysematous osteomyelitis (EO) is a type of disease caused due to gas-forming bacteria. It is an uncommon disease that is hard to be identified by clinical practice and to fully characterized by the process of imaging. It is a rare, acute, infectious, and possess life-threatening conditions with the radiographic appearance of intraosseous gas present in communication between the bone and the air [27].

Calcaneal osteomyelitis is a serious disease that occurs mainly in a diabetic foot leading to the amputation of the abrasion area [20]. The process to restrict the occurrence is to remove the infected bone with the help of surgical method. Improper removal of the affected bone may repeat the occurrence of the disease, and there should be a proper method for the preservation of the bone to restrict from the failure of the stability of the residual foot. Covering of the soft tissue is the most crucial step in this method. In this case, the removal of the area of abrasion in the bone always depends on the experience of the surgeon.

**3. USFDA Approved Drugs Used for the Treatment for Osteomyelitis:** Vancomycin drug is used for its slow bactericidal activity, which bonds with D-alanyl-D-alanine and acts as a precursor for peptidoglycan in preventing or restricting the cell wall synthesis of gram-positive bacteria. For bacteria such as *Staphylococcus aureus*, the dosing of the drug is equivalent to 2 mg/L. In adults, the appropriate dosing for minimum inhibitory concentration (MIC) is equivalent to 1 mg/L [36-37]. Patients with Acute Hematogenous Osteomyelitis (AHO) have a high risk of Methicillin-resistant *Staphylococcus aureus* (MRSA) Osteomyelitis should be treated with Vancomycin.

Clindamycin comes under the lincosamide type of antibiotics that exhibits the activity, which is concentration-dependent, which occurs due to the binding the 50S ribosomal subunit and inhibiting protein synthesis. Although it is thought as a bacteriostatic antimicrobial, it has been shown bactericidal activity against *S. aureus* that is best predicted by AUC [38-39]. The acceptable dosing of clindamycin for the treatment of osteomyelitis caused by *Staphylococcus aureus* is 0.5 mg/L. Clindamycin can be used for pediatric patients, dealing with AHO, where the area affected by *Staphylococcus aureus* is less.

Daptomycin is said to be a concentration-dependent, falls in a group of cyclic lipopeptide antimicrobial agents, which acts on the bacterial cell membrane by the activity of depolarization. It is used to treat MRSA for its high activity against the disease, with dosing equivalent to 1 mg/L [40-42].

The treatment of Osteomyelitis with the help of antibiotics, which are administrated locally has been used for many years and is believed to be safe and effective as per many surgeons [45]. Antibiotics loaded with Calcium sulfate (CAS) materials are generally used for the treatment of bone defects after the removal of the infected bone, and pathological fractures are seen in about 5% of patients with the disease [46-48].

Fluoroquinolones are used for the treatment of Osteomyelitis for its extremely good activity against pathogens causing defects and toxicity. They are chosen for the treatment due to their pharmacokinetic (PK) profile, high bioavailability (60-99%), moderate protein binding (20–60%) and good tissue penetration [43]. Their ability to penetrate through the cell helps in the treatment of bone infections, as per *in-vitro* studies, because

*Staphylococcus aureus* can penetrate the cell and restrict the formation of new bone [44]. Second-generation fluoroquinolone, such as Ciprofloxacin, is used for its high activity against both gram-positive and gram-negative bacteria. It also can be used against many problems such as infection in bone and joints, infections in the respiratory tracts, infections in the urinary tract and topical regions.

Aminoglycoside antibiotics, such as Gentamicin is used mainly in higher form for the treatment of many infections because it provides wide bacterial spectrum. Although, after oral administration, it shows lower bioavailability and have low penetration power through the cell. When gentamicin is administered parenterally, it gets excreted rapidly due to glomerular filtration. Repetitive dose administration of the drug may also cause renal accumulation and nephrotoxicity. Longer administration of the drug may also cause ototoxicity due to the formation of free radicals [49-50].

**4. Various Treatment of Osteomyelitis according to USFDA Guidelines:** Treating with the antibiotics is important in osteomyelitis cases, some of the problems caused during treatment are at the interface of impaired vascularity that occurs in the infected area of the bone. In the case of Chronic Osteomyelitis, the formation of Sequestra (devasted part of the infected bone) can be seen, which cannot be affected by leukocytes or which cannot be treated by antibiotics for their less concentration.

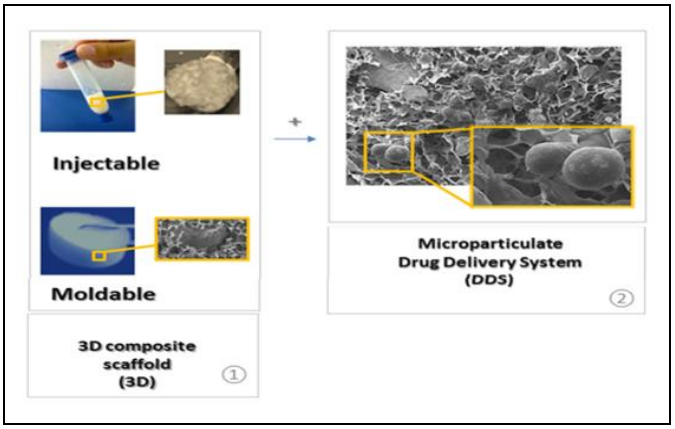
Some of the current treatment methods are:

**An Intramedullary Nail Coated Nanoparticles with Antibiotic and its Growth Factor: An Individualized Art for the Treatment of Chronic Osteomyelitis with Formation of Bone Defects:** In this study, the treatment of Chronic osteomyelitis has been taken into consideration, with PMMA. In the treatment of chronic osteomyelitis, comprehensive and aggressive surgical procedures are required, including removal of infected or dead bone with surgical methods, removal of Sequestrum(a fragment of dead bone detached from adjoining sound bone), curettage, and dead-space management [69, 70]. If there is no sufficient surgical treatment, the infection will be stable, and there will repeated occurrence of the infection. The extensive removal of the infected bone may also lead to the formation of a considerable large area cavity or space in the bone that will require many procedures to fill **Fig. 1** [69, 71]. For Chronic Osteomyelitis, Polymethyl methacrylate [PMMA] beads, saturated with antibiotics, are widely used for the treatment, instead of having several clinical limitations such as, PMMA is non-biodegradable in nature, it needs second surgical intervention for the removal of the cemented material, occurrence of initial burst due to its insufficient antibiotic release and lack of mechanical stability [51-56]. This method can restrict the antibiotic, which leads to biofilm formation, and absorption of methyl methacrylate (MMA) monomers may cause moderate toxicity due to the carboxylesterase-mediated conversion of MMA to methacrylic acid [52].

**Formulation and Development of Composite Biodegradable Scaffolds as Antibiotic Delivery System and also a Regenerative Device for Bone:** In this study, Biodegradable scaffolds have been taken into consideration for the treatment of Osteomyelitis. One of the therapeutic treatment is bone grafting, which is carried out by introducing natural bone substitute in the area of abrasion. The major perspective for this study is to carry out bone grafting, combined with a drug delivery system (3D-DDs). The 3D-DDs can be taken as injectable or moldable, which composed of a biocompatible, biodegradable polymer, with a combination of decellularized bone matrix (Bovine Bone substitute- BBs) and with the antibiotic drug, gentamicin as considered in this study, which is encapsulated and formed as a biodegradable microparticle.

The moldable 3D scaffold is formulated in such a way that it can be separated by cutting into desirable length, hydrated and can be remodeled by a surgeon according to their specification, for fitting and curing the bone defect. The injectable composite scaffold is obtained with the method of lyophilization and also results in high porosity, and the obtained spongy structure of lyophilized scaffolds allows fast hydration of scaffold in blood or any physiological fluids of the body, without any change in the physical structure. Certain advantages of 3D-DDS are, it will ready to be used at any time, administration can be done through

cannula or can be administered into the defected part through surgical procedures, easy to insert into irregular body spaces or cavities caused due to the disease or caused due to fracture and perfectly fir in the defected site of the bone, keeping the physical integrity stable throughout [64].




**Treating Osteomyelitis of Major Limb Amputations with a Modified Lautenbach Technique:** Amputation of the defected lower is defined as the removal process of the defected area of the leg above the knee, through the knee, or below the knee [65]. Continuous amputation method in the case of chronic osteomyelitis has considered easy way than the resection of the bone or defected areas. Modified Lautenbach technique is used to avoid the problems which may occur during the amputation of the affected area of the bone. Charles Lautenbach (Johannesburg, RSA), the man behind the technique, according to his original work, described the method as complete removal of all vascular and infected tissue which are present in the area of the bone and also the other parts which in infected in the medullary canal, through surgical methods. The entire area of the medullary canal should be washed with saline water until there are any materials that are found, which can be the cause of further defects. The infected area will be cleaned, and space is created for the insertion of suction-irrigation tubes, which is used for the antibiotics to be administered or to be inserted into the defected areas of the bone, caused due to the disease [66].

This attempt will allow the antibiotics to reach directly to the infected areas and more suitable than hematogenous delivery of the antibiotics into an area of abrasion. This method also has some limitations as it will decrease the concentration of the required antibiotic, which will be needed at the site of abrasion or the defected area. The use of Streptokinase is also described as a method in which it can be used in the irrigation tubes to restrict from clotting and blocking, which might occur during the method of administration in the tube, without causing any disturbance to the blood flow [67]. Lautenbach has also described the use of a suction-irrigation system to administer antibiotics locally into the defected area and to diminish the disease-causing matter. In this study, a modified technique has been used for the treatment of diaphyseal osteomyelitis, which involves the surgical of the defected bone from the intra-medullary compartments, without the use of suction-irrigation tubes, which is used for the administration of local antibiotics.

**Bioactive Hydrogels for Bone Regeneration:** Bioactive hydrogels are polymer scaffolds with several advantages for repairing bone defects. Hydrogels are the formation of three-dimensional hydrophilic polymer chains, which are having high mechanical strength and provides nutrient environments suitable for the growth of endogenous cells. They provide or act as an extracellular matrix (ECM) of the bone, which makes them enclose or entrap the bioactive molecules or cells. Due to its network structure, the hydrogels can restrict the loss of proteins or cells and controls the desired release of the materials required for the treatment [69]. Being extensively absorbable, the hydrogels can get linked to the surrounding tissues, restricting or giving a less chance of complicated surgical operation and reduce the possibility of inflammation [68].

**Formulation and Development of Vancomycin Incorporated Chitosan/Gelatin Coatings Coupled with the $TiO_2$–Srhap Surface Modified Cp-Titanium for the Osteomyelitis Treatment:** As discussed earlier in the article, vancomycin is a type of amino glycopeptide and most commonly used clinically for the treatment of chronic osteomyelitis. This type of glycopeptide acts at the site of receptor levels, which results in blocking the growth of the bacteria [72]. A major challenge in the case of implant material is to provide a bio-interactive surface that will restrict or obstruct the growth site bacterial agents and increase the biological activity.

In this study, we can see the surface modification of Cp-Ti, which is done due to electrophoretic deposition (EPD) of a double layer. In the first layer we can see a combination of $TiO_2$ metal oxide and Sr-HAP ceramic oxide, where the reason for the addition of metal oxide is to increase electrochemical resistance, which will minimize the occurrence of leaching which occurs due to the wear, whereas Ti metal has less wear resistance and while annealing, it should give unmatched thermal coefficient expansion [73, 74]. The second layer is a formation of the drug, *i.e.* vancomycin, which is encapsulated with chitosan/gelatin coating. The reason for choosing EPD as a polymer is to avoid the use of cross-linkers [75]. Micro nano-topography of the coated second layer is done to get the best dual objectives of surface, and the first layer will increase the integration of the metal surface with the biological environment [76]. So, the double-layer coated sample can be used in one ideal metallic implant, for the treatment

**Single Stage Treatment of Diabetic Calcaneal Osteomyelitis with an Absorbable Gentamicin-Loaded Calcium Sulphate/Hydroxyapatite Bio-composite: The Silo Technique:** In recent studies, it has been seen that using of Calcium Sulphate (CAS), combining with hydroxyapatite (HA) in a synthetic and injectable mixture has become "the new era bone substitute" [77]. The combination is also added with the antibiotics, which is 175 mg gentamycin in 10 ml CAS/HA (Cerament G; Bone support, Lund, Sweden). In the cases of chronic osteomyelitis, it has been shown that Cerament G biocomposite is extensively used for dead space management [78]. For the treatment of chronic calcaneal osteomyelitis, many authors have considered the Silo technique, with the used of Cerament G. This method provides limitations to repeated surgical procedures for the removal of defected bones and also gives easy way of using antibiotics, which can be inserted with the local delivery administration into the deep bone to destroy the microscopic foci, which are the major cause for the infection.

**Outpatient Treatment of Osteomyelitis with Telavancin:** Some of the Osteomyelitis diseases are treated with OPAT method which requires prolonged administration antimicrobials intra-venously, moreover, osteomyelitis also requires many surgical interventions and produce difficult in the therapeutic challenges [79, 80]. It has been observed that treatment with OPAT has shown clinical failures in >30% of osteomyelitis patients [81]. Gram-positive bacteria are the most common, with *Staphylococcus aureus* accounting for the in many cases, the presence of Gram-positive bacteria, such as Staphylococcus aureus have taken into account [81, 82]. Telavancin is used as an antibiotic, which is a group of lipoglycopeptide which is administered intravenously. It is approved in foreign countries, such as the USA for the treatment of adult patients, dealing with complicated skin and skin structure infections (cSSSIs) caused by Gram-positive pathogens [83]. Telavancin is approved in European countries for nosocomial pneumonia caused due to MRSA and in Canada for the treatment of HABP/VABP and cSSSI majorly caused due to Gram-positive pathogens [85].

## 5. Future Prospects for the treatment of Osteomyelitis:

**MRI of Acute Osteomyelitis in Long Bones of Children: Pathophysiology Study:** Acute osteomyelitis (AOM) is a type of infection spreads hematogenously in the bone causing defects. Diagnosis of AOM is done with help of imaging method. Although, imaging methods for scanning the bone defects are used majorly and very important for diagnosis, so it is replaced with magnetic resonance imaging (MRI), for the method gives proper analytical details for the tissue involvement and it is having a non-irradiating character. It is almost 98% sensitive in nature and its specificity is about 92% [87].

The described pathophysiology of acute osteomyelitis by trueta [88] in children, which carried out more than 60 years ago has shown inoculation at the metaphysis, which is the primary cause, which also leads to swelling of the interior parts of the bone, that can spread to the formation of subperiosteal abscess. This description of pathophysiological of AOM was questioned by Labbé *et al.*, [89] when they came across with ultrasonography study that the primary cause of AOM is actually for vaccination in the internal bone. But in recent terms, no study has carried out the investigation on AOM pathophysiology using modern techniques.

Hence, a study has been carried out with an important objective to check the possibility to clarify the pathophysiology of AOM by performing MRI in the early stages. Another objective of this study is to see if there is any abnormal consequences or problems in the MRI readings, which can occur due to the age of the patient, location of the bone, nature of the causative bacteria, any difficulty in the progression with the treatment and any occurrences of complications.

**Osteomyelitis: Recent Advances in Pathophysiology and Therapeutic Strategies:** The disease Osteomyelitis holds within different types of disease mechanisms, which comes under three generally accepted categories, such as: spreading of hematogenous bacterias, contamination and vascular insufficiency associated infection [90]. The characteristics of each category can be summarized as follows: (1) Primary hematogenous spread of bacteria mainly afflicts the metaphysis of skeletally immature patients or vertebral bodies at all ages, although infection at other locations may occur [91, 92]. (2) Contiguous infection is usually spread from a contaminated site, most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with an orthopedic implant. (3) Vascular or neurologic insufficiency associated osteomyelitis results from the poor blood supply, diabetic wounds, loss of protective sensation and altered immune defenses, commonly affecting the lower extremity.

**CONCLUSION:** By understanding the current trends, the administration of various antibiotics as dosage forms can be classified and analyzed. Among various types, treating Chronic Osteomyelitis using antibiotics in different dosage forms such as Polymethyl methacrylate [PMMA] beads has given proper results in the treatment of the disease and restricted the mutations of the disease-causing bacteria.

The composite biodegradable scaffolds comprising of Bovine Bone Substituent acted as a matrix to the bone to help the delivery of the drug to the bone and act as a bone glue staying in the liquid form, so as to solidify with a change in the body temperature. Using a modified Lautenbach Technique for the limb amputation had been an eye-opener for surgeons and physicians to treat the disease and also to restrict spreading of the disease to entire bone tissue. Bioactive hydrogel polymers encapsulated in scaffolds help to carry the drug to disease area and protect the bone from the activity of the bacteria causing the disease.

The silo technique has given the surgeons a chance to treat Diabetic Calcaneal Osteomyelitis. The use of an antibiotic such as gentamicin will cease the disease by activating on the bacteria causing it and reduces the chance of repetitive surgical operations. The current methods are used for the treatment of Osteomyelitis cases in various countries. In India, osteomyelitis cases are very less, and the preferred drug formulations are used for the bone regeneration process.

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