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Review

The Use of Calcium Phosphate Bioceramics for the Treatment of Osteomyelitis

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Abstract: Bone infections, particularly osteomyelitis, present significant clinical challenges due to their resistance to treatment and risk of progressing to chronic disease. Conventional therapies, including systemic antibiotics and surgical debridement, often prove insufficient, especially in cases where biofilms form or infection sites are difficult to access. As an alternative, calcium phosphate bioceramics have emerged as a promising strategy for treating bone infections. These materials offer key advantages such as biocompatibility, osteoconductivity, and the ability to be engineered for controlled drug delivery. Calcium phosphate bioceramics can serve as scaffolds for bone regeneration while simultaneously delivering antibiotics locally, thus addressing the limitations of systemic therapies and reducing infection recurrence. This review provides an overview of osteomyelitis, including its pathogenesis and conventional treatment approaches, while exploring the diverse therapeutic possibilities presented by calcium phosphate bioceramics. Special attention is given to hydroxyapatite, tricalcium phosphate, and their composites, with a focus on their therapeutic potential in the treatment of bone infections. The discussion highlights their mechanisms of action, integration with antimicrobial agents, and clinical efficacy. The dual capacity of calcium phosphate bioceramics to promote both bone healing and infection management is critically evaluated, highlighting opportunities for future research to address current challenges and enhance their clinical application in orthopedics and dentistry. Future research directions should focus on developing calcium phosphate bioceramic composites with enhanced antibacterial properties, optimizing drug-loading capacities, and advancing minimally invasive delivery methods to improve clinical outcomes. Further in vivo studies are essential to validate the long-term efficacy and safety of calcium phosphate bioceramic applications, with an emphasis on patient-specific formulations and rapid prototyping technologies that can personalize treatment for diverse osteomyelitis cases.

Keywords: osteomyelitis; hydroxyapatite; calcium phosphates; bone infection control

Citation: Oliveira, C.S.F.; Negut, I.; Bita, B. The Use of Calcium Phosphate Bioceramics for the Treatment of Osteomyelitis. *Ceramics* **2024**, *7*, 1779–1809. https://doi.org/10.3390/ceramics7040113

Academic Editor: Eric Champion

Received: 24 September 2024
Revised: 15 November 2024
Accepted: 20 November 2024
Published: 25 November 2024

1. Introduction

Osteomyelitis, a common type of orthopedic infection, is characterized by inflammation and bone destruction caused by microbial infections. This condition often results from local infection spread following trauma, orthopedic surgery, or joint replacement. The infection may be confined to a specific area of the bone or involve multiple regions such as the bone marrow, cortex, periosteum, and surrounding soft tissues [1,2]. Once pathogens invade the bone, they release proteolytic enzymes and free radicals that trigger inflammation and damage nearby tissues, which in turn leads to increased blood flow to the infected area and heightened bone destruction. This process also compromises the permeability barriers, making it more difficult for antimicrobial agents to reach the infection site [3].

Acute osteomyelitis develops swiftly, often within days or weeks following an infection or injury, and may present symptoms such as pain, fever, swelling, and redness around the infected area. If not managed promptly and effectively, acute osteomyelitis can progress to chronic osteomyelitis, a more persistent and complex form of the disease that can last for months or even years. Chronic osteomyelitis is particularly challenging to treat, as it often involves recurring infections, the presence of necrotic bone tissue, and biofilm formation, which shields bacteria from both antibiotics and the immune system [1–3]. The impact of chronic osteomyelitis on patients can be profound, leading to continuous pain, loss of function, and in severe cases, life-threatening complications such as bone necrosis, septicemia, or widespread infection. These complications may necessitate extensive surgical interventions, including debridement to remove infected tissue or, in extreme cases, amputation. The physical and psychological toll on patients can be significant, as chronic osteomyelitis often results in permanent disability or reduced quality of life due to mobility issues and ongoing infection risk [1–3].

Clinically, osteomyelitis presents considerable challenges in terms of treatment and patient management. Conventional therapy generally requires the prolonged use of high-dose antibiotics to control the infection. However, achieving effective antibiotic concentrations at the infection site within bone tissue is difficult due to poor vascularity, particularly in chronic cases. The treatment is often supplemented by repeated surgical debridement procedures to remove necrotic bone and infected tissue. These procedures, while necessary, can weaken the structural integrity of the bone, prolong recovery, and increase the risk of reinfection. Additionally, long-term antibiotic use poses risks of systemic side effects, such as nephrotoxicity and antibiotic resistance, further complicating patient management [1–3].

The need for improved treatment options in osteomyelitis is evident, as current approaches are often invasive, lengthy, and associated with considerable morbidity. Emerging strategies, including localized antibiotic delivery through calcium phosphate bioceramic (CaP) carriers and bioactive materials, aim to address these limitations by delivering sustained, high-concentration antibiotics directly to the infection site, enhancing bone healing while reducing systemic side effects. This targeted approach could provide more effective and less invasive options for patients, potentially transforming the clinical management of both acute and chronic osteomyelitis [1–3].

Since the discovery of penicillin in 1928, antibiotics have been widely employed to effectively treat a variety of infectious diseases [4]. However, the overuse of antibiotics has contributed to the rise in bacterial resistance [5]. It is estimated that approximately 700,000 people die annually from drug-resistant bacterial infections, with this figure predicted to escalate to 10 million by 2050 if more effective treatments are not developed [6]. The primary pathogens responsible for osteomyelitis include Gram-negative bacteria such as *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Escherichia coli* (*E. coli*), as well as Gram-positive bacteria, namely *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (*S. epidermidis*), *Enterococcus* and *Streptococcus* species [3]. Among these, *S. aureus* is the most common causative agent of osteomyelitis, contributing to bone destruction through mechanisms such as inducing osteoblast apoptosis, promoting osteoclast activation, and secreting toxins [1,5,7].

Notably, more than 30% of *S. aureus*-induced osteomyelitis cases are linked to methicillin-resistant *S. aureus* (MRSA) [1,5]. Conventional antibiotic therapies for osteomyelitis encounter several critical limitations, including issues with solubility, the potential for overdose, and cytotoxicity, which restrict their effectiveness and safety. Antibiotics often struggle to achieve sufficient concentration at the infection site due to poor solubility, especially within the dense bone tissue. This can lead to subtherapeutic dosing, reducing efficacy and increasing the risk of antimicrobial resistance as bacteria survive and adapt. On the other hand, high doses required to reach therapeutic levels within bone can result in systemic toxicity, posing serious health risks such as nephrotoxicity, hepatotoxicity, and gastrointestinal issues. These challenges emphasize the urgent need for more targeted and controlled antimicrobial treatments that not only enhance efficacy at the infection site but

also reduce adverse side effects and the risk of resistance, paving the way for safer, more effective osteomyelitis therapies [3].

To address the challenges associated with osteomyelitis treatment, significant advancements have been made in recent years. Novel antimicrobial therapies, including the use of metals [8], chitosan (Cs) [9], antimicrobial peptides (AMPs) [10], and bacteriophages [11], have been developed and are being increasingly applied. Additionally, local delivery systems utilizing biological carrier materials or specialized therapeutics have been introduced to provide the controlled release of antimicrobial agents directly at the infection site. This targeted approach not only enhances the effectiveness of infection treatment but also reduces the side effects associated with systemic antibiotic therapy and promotes bone regeneration [12].

Carrier materials, particularly calcium phosphate (CaP), have proven to be highly effective in the localized treatment of osteomyelitis. CaP are extensively used due to their excellent biocompatibility and osteoconductive properties, which facilitate bone cell attachment and support new bone formation. These materials allow for targeted antibiotic delivery directly at the infection site, enhancing therapeutic efficacy while minimizing systemic side effects. Their ability to integrate with bone tissue makes them ideal candidates for osteomyelitis treatment, combining infection control with the promotion of bone regeneration [13].

These materials not only serve as scaffolds and fillers for bone regeneration but also act as carriers for antimicrobial agents, ensuring controlled and sustained release at the infection site [14]. By delivering high concentrations of antibiotics directly to the affected area, CaP-based systems enhance the therapeutic outcome while minimizing systemic side effects [14]. Moreover, the bioactive nature of CaP, such as hydroxyapatite (HA) and beta-tricalcium phosphate (β-TCP), plays a significant role in promoting bone healing by creating an environment conducive to cell proliferation and tissue regeneration. CaP not only supports the adhesion and growth of osteoblasts and the cells responsible for bone formation, but it also encourages the formation of a mineralized extracellular matrix that is essential for new bone tissue development. This bioactivity makes CaP particularly valuable in treating bone infections like osteomyelitis, where both infection control and bone regeneration are critical for successful outcomes [14,15].

The surface properties of CaPs enable them to interact with surrounding biological tissues, promoting cellular responses that aid in the repair of damaged bones. For instance, when implanted in bone defects, CaPs can bond directly with bone tissue, providing a stable scaffold that facilitates natural bone remodeling [14,15]. The gradual dissolution of CaP releases essential ions, such as calcium and phosphate, which are critical for bone mineralization and serve as building blocks for new bone growth [14,15]. This ion release also creates a local environment that supports angiogenesis—the formation of new blood vessels—thereby improving blood supply to the healing site and supporting sustained tissue regeneration [15]. The combination of drug delivery and bone regeneration in a single platform further enhances the clinical potential of these materials [15].

Herein, the paper provides an in-depth review of the role of CaPs in bone regeneration and infection control, with a particular focus on osteomyelitis. After discussing the pathophysiology of osteomyelitis and the challenges it presents in clinical management, we explore the various CaP materials, such as HA, TCP, and their composites. The paper presents the synthesis methods, structural properties, and biomedical applications of these materials, emphasizing their biocompatibility, osteoconductivity, and antimicrobial potential. Special attention is given to the integration of CaPs into localized drug delivery systems, where their porous structures enable the controlled release of therapeutic agents, such as antibiotics, to the infected site. Additionally, the review highlights recent advancements in CaP coatings and scaffolds that further enhance their therapeutic capabilities, particularly in treating chronic bone infections. By addressing both infection control and bone regeneration, this paper aims to provide a comprehensive overview of the transformative role of CaPs in modern orthopedics and dentistry. The findings presented here

underscore the promise of CaP materials in improving patient outcomes and advancing clinical practices in bone infection management.

2. Overview of Osteomyelitis

Osteomyelitis is a serious orthopedic condition characterized by an infection of bone tissue caused by pathogenic microorganisms [16]. This condition often arises from skin wounds or incision, bone fractures, surgical procedures, or the spread of infection through the bloodstream from other parts of the body [17]. If not treated promptly, the infection may lead to significant inflammation, destruction of bone tissue, and potential necrosis.

Osteomyelitis presents an overall incidence of 21.8 cases per 100,000 person-years [18] and can affect individuals across all age groups, but certain populations are at higher risk. Children are more susceptible to acute osteomyelitis, which typically affects the long bones, while adults, particularly those with diabetes, compromised immune systems, or poor vascular health, are more prone to developing the chronic forms of the disease [19].

The symptoms of osteomyelitis commonly include severe pain, fever, and swelling in the affected area, though these symptoms can vary depending on the infection's location and severity [20]. Diagnosis usually involves a combination of clinical examination, imaging studies, and laboratory tests to identify the causative organism.

The conventional treatment for osteomyelitis typically involves the use of antibiotics or antifungal medications. In cases where the infection has caused significant damage, surgical intervention may be necessary to remove infected and necrotic bone tissue [21]. However, the increasing issue of bacterial resistance has diminished the effectiveness of traditional antibiotics, prompting a shift towards the development and use of more advanced antibacterial therapies.

Treatment for osteomyelitis is often prolonged and challenging, largely due to the bone's dense structure and limited blood supply, which difficult the effective delivery of medication and hinder the immune system's ability to fight the infection [22]. Despite notable advancements in medical technology and treatment options, osteomyelitis remains a significant challenge, marked by high rates of recurrence, considerable morbidity, prolonged hospitalizations, and substantial healthcare costs [21].

2.1. Pathogenesis of Osteomyelitis

Surgical debridement, when combined with local antibiotic application and sustained-release systems, has been shown to address these challenges and significantly improve the cure rate of chronic osteomyelitis [23]. Nevertheless, despite advancements in both surgical and antibiotic treatments, the long-term recurrence rate of chronic osteomyelitis remains at 20–30% [24].

Understanding the pathogenesis of osteomyelitis is crucial, as the infection often involves pathogens like *Staphylococcus aureus* (*S. aureus*) and methicillin-resistant *S. aureus* (MRSA). These infections trigger an inflammatory response, leading to pus formation, bone tissue destruction, and potentially bone necrosis [22]. Due to these complexities, early and effective treatment is critical to prevent severe complications such as chronic infection, abscess formation, sepsis, and even amputation. However, treatment remains difficult, as the dense structure of bone and its limited blood supply impede the delivery of immune cells and medications to the site of infection.

Healthy bones are usually resistant to infection. However, they can become vulnerable when exposed to a large inoculum of bacteria, often due to trauma, ischemia, or the presence of foreign bodies [2]. These conditions expose bone tissue sites where microorganisms can adhere, increasing the risk of infection.

The pathogenesis of osteomyelitis begins when bacteria, fungi, or other pathogens infiltrate bone tissue. Common causative agents include Gram-positive bacteria such as *S. aureus*, *S. epidermidis*, *Enterococcus* spp., and *Streptococcus* spp., as well as Gram-negative bacteria like *E. coli* and *P. aeruginosa* [3,17]. Among these, *S. aureus* is the most prevalent, responsible for approximately 75% of all osteomyelitis cases [25]. *S. aureus* typically causes

bone destruction by inducing osteoblast apoptosis, osteoclast formation, secreting toxins, and forming biofilms [1,5]. *S. aureus* biofilms on necrotic bone and implant surfaces are particularly difficult to treat and eradicate because they restrict antibiotic diffusion to bacterial cells, inhibit immune cell penetration, and resist mechanical disruption [22]. Additionally, the bacteria within a biofilm exhibit metabolic diversity due to gradients in nutrient and oxygen availability, which promotes the development of small colony variants and persisted cell populations [22]. These adaptations further complicate the treatment by enhancing the bacteria's ability to survive in hostile environments. Among cases of *S. aureus*-induced osteomyelitis, over 30% are associated with methicillin-resistant *S. aureus* (MRSA) [5]. A study reported that MRSA infections are widespread globally, resulting in approximately 19,000 deaths and 360,000 hospitalizations annually in the United States alone [26].

Once the pathogen reaches the bone, it triggers the body's immune response, leading to inflammation [3]. As the immune system fights the infection, white blood cells gather at the site, releasing enzymes that can inadvertently damage surrounding bone tissue [22]. This process results in the formation of abscess, which can create pressure within the bone and further compromise the blood supply (Figure 1). As the infection progresses, the bone tissue may begin to die due to the lack of adequate blood flow, a condition known as bone necrosis. The dead bone, called sequestrum, can act as a reservoir for infection, making it difficult for antibiotics and the immune system to clear the infection [22].

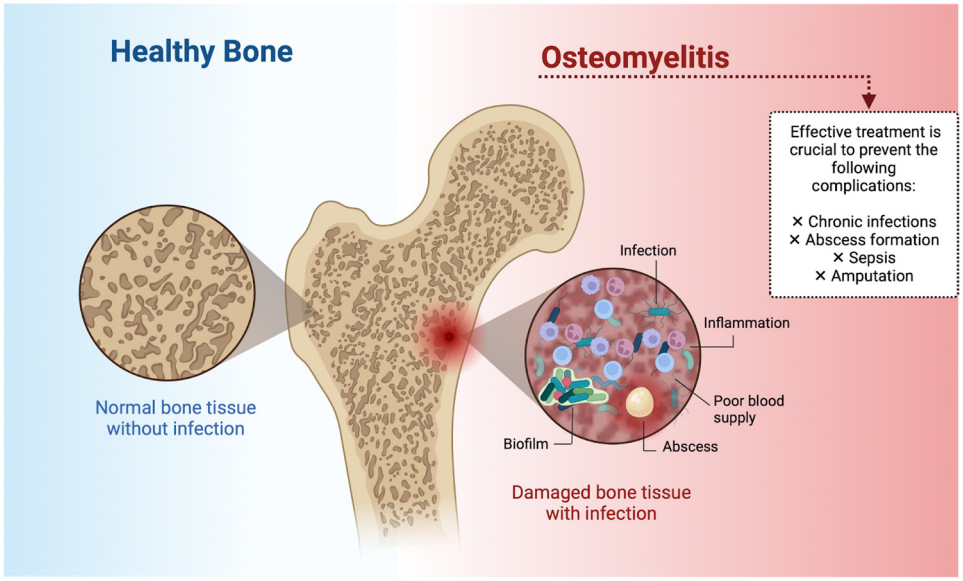

Figure 1. Differences between healthy bone and bone with osteomyelitis. The illustration contrasts healthy bone tissue with bone affected by osteomyelitis. The left side, labeled "Healthy Bone," displays normal bone tissue free from infection. In contrast, the right side, labeled "Osteomyelitis," shows bone tissue that has been compromised by infection. Key features of the infected bone include inflammation, biofilm formation, abscesses, and reduced blood supply. The image underscores the critical need for effective treatment to avoid severe complications, such as chronic infections, abscess formation, sepsis, and the potential need for amputation. Created in BioRender. Oliveira, C. (2024) https://BioRender.com/x05t804.

Despite similarities, the infection can manifest in various forms depending on its duration and severity. Osteomyelitis is then categorized as follows: (i) acute, characterized by rapid onset and severe symptoms; (ii) subacute, with a slower progression and milder symptoms; and (iii) chronic, involving a long-standing infection with recurring symptoms and persistent bone damage [20]. In severe cases, osteomyelitis can lead to limb necrosis, dysfunction, or even sepsis, potentially necessitating surgical interventions, such as amputation and resulting in permanent disability [21].

Currently, the rate of cure for acute osteomyelitis can reach up to 80% with early diagnosis and appropriate antibiotic therapy [27,28]. However, in cases of chronic osteomyelitis, local bone loss and soft tissue insufficiency contribute to ischemic sclerosis of the affected bone. These factors make it difficult to achieve effective bactericidal concentrations with systemic antibiotics alone.

2.2. Strategies for Treatment

The treatment of osteomyelitis typically involves the administration of antibiotics or antifungal medications. However, the therapeutic approach depends on the specific type of osteomyelitis. Acute osteomyelitis is generally treated with antibiotics alone, while chronic osteomyelitis often requires surgical debridement alongside antibiotic therapy for effective treatment. In fact, the successful management of osteomyelitis usually requires a multidisciplinary approach, involving collaboration between orthopedic surgery, infectious disease specialists, and plastic surgeons. In more complex cases, particularly those with significant soft-tissue loss, the expertise of vascular surgeons becomes essential for providing comprehensive care.

In this sense, osteomyelitis remains a significant challenge in clinical practice due to its complex pathophysiology and the difficulty of delivering sufficient antibiotic concentrations to the infection site. To address these obstacles, a variety of antibiotic delivery strategies using different routes for administration and specialized materials designed for targeted drug delivery have been utilized in the treatment of osteomyelitis. Figure 2 illustrates various antibiotic delivery strategies for osteomyelitis treatment, highlighting both systemic and localized approaches.

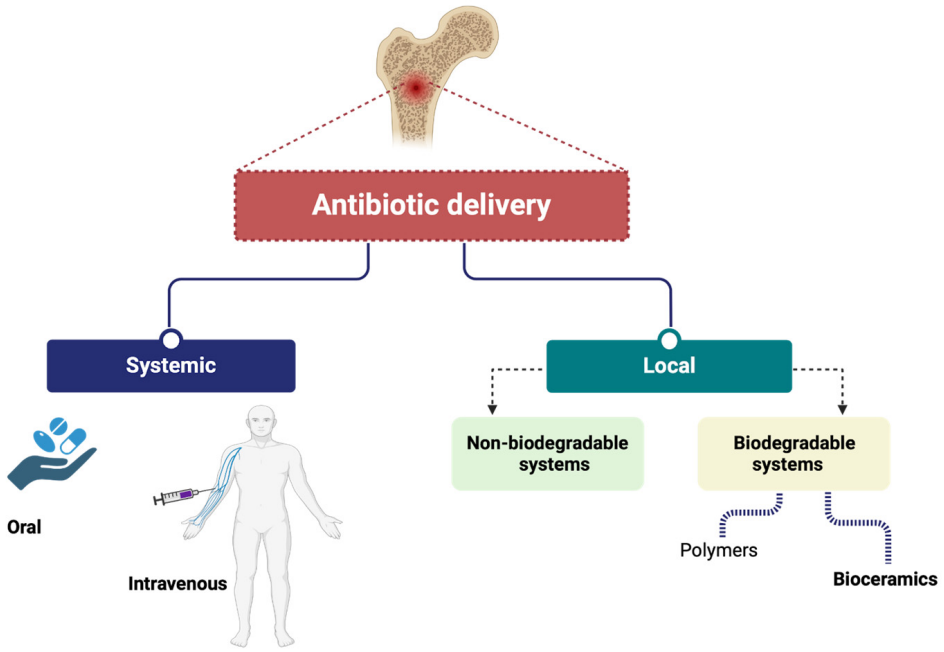

Figure 2. Different strategies for antibiotic delivery for the treatment of osteomyelitis. Created in BioRender. Oliveira, C. (2024) https://BioRender.com/d84y224.

2.2.1. Short Overview of Oral, Intravenous, and Surgical Treatments

Treatment of osteomyelitis typically involves a combination of antibiotic and surgical strategies, with antibiotic options including both oral and intravenous (IV) routes, selected based on infection severity, pathogen profile, and patient suitability. Landmark studies, such as the oral versus intravenous antibiotics trial, have demonstrated that oral antibiotic therapy can be as effective as IV therapy in many cases, showing comparable one-year success rates for complex orthopedic infections, while reducing hospitalization time and

healthcare costs [29,30]. For pediatric osteomyelitis, oral antibiotics have similarly proven effective, with fewer complications compared to catheter use in IV therapy [6].

Oral agents like fluoroquinolones, clindamycin, and linezolid offer strong bone penetration and efficacy against common osteomyelitis pathogens, including *S. aureus* and MRSA, and are particularly effective following an initial IV course or for patients without absorption limitations [6]. By contrast, IV antibiotics—such as vancomycin (VAN), daptomycin, and cefepime—deliver high concentrations directly to the bloodstream, which is essential for acute or severe cases and those unsuitable for oral therapy [31,32].

Combining systemic antibiotics with local delivery, such as antibiotic-loaded bone cements or beads, allows for high local antibiotic concentrations, improving bacterial eradication at the infection site and proving especially useful for chronic osteomyelitis and implant-related infections [33]. However, IV treatment also poses risks, including catheter-related infections and potential organ toxicity, necessitating careful monitoring. Shorter IV courses followed by oral therapy have shown a reduced risk of liver and kidney complications without increasing recurrence rates [34,35].

Surgical intervention remains crucial for effective osteomyelitis management, particularly in complex or refractory cases. Procedures such as debridement, which removes biofilm and necrotic tissue, are essential to control infection but create dead spaces that need filling to prevent re-infection [36]. These spaces are often filled with bone grafts [37] or antibiotic-loaded biomaterial spacers for localized drug delivery [38]. Studies indicate that early surgical intervention can significantly improve outcomes, and the use of antibiotic-loaded materials can aid in achieving sustained infection control [38].

2.2.2. Localized Bone Drug Delivery Using Biomaterials

Local osseous drug delivery has become a cornerstone in treating bone infections, particularly osteomyelitis. This approach allows for the direct delivery of high concentrations of antibiotics to the infection site, reducing systemic exposure and minimizing side effects [39]. Over time, these techniques have evolved significantly, moving from early methods like the "closed irrigation" systems of the 1960s to more sophisticated biodegradable and non-biodegradable carriers used today [32].

Biomaterials designed for local drug delivery offer a highly targeted approach for managing bone infections, delivering high concentrations of antibiotics directly to the infection site [40]. This ensures effective antibacterial action at the precise location needed, making it particularly advantageous for treating localized infections such as osteomyelitis. By concentrating an antibiotic to a specific site, local delivery can disrupt biofilms, overcoming their protective barriers, which is crucial for biofilm-associated infections. However, maintaining a consistently adequate concentration at the infection site can be challenging due to the nature of the drug release mechanism. Variations in release profiles may lead to fluctuations in local antibiotic levels, which could reduce efficacy over time if not carefully controlled [41]. In CaPs, HA and its various derivatives, including composites, mixtures, and doped forms, have gained importance in the treatment of osteomyelitis due to their exceptional biocompatibility rate, osteoconductivity, and capacity for functionalization with many antibacterial agents [42,43].

A major benefit of local drug delivery systems is their potential to minimize systemic toxicity. By confining the antibiotic to the targeted area, these systems limit body-wide exposure, reducing risks associated with systemic side effects, such as gastrointestinal distress or nephrotoxicity. However, poor tolerance or insufficient control over the local release can sometimes lead to unintended systemic absorption, potentially causing side effects despite the localized application. Effective design and formulation are critical to ensure that the therapeutic benefits outweigh any potential risks of systemic exposure [44].

In addition to infection control, biomaterials for local delivery can promote bone regeneration by combining antibiotics with osteoconductive agents, such as bone graft materials [45]. This dual action enhances the healing process, supporting both infection management and bone repair, which is essential for effective recovery in bone-related

infections. However, the formulation of these systems requires careful balancing to ensure antimicrobial efficacy while also fostering an environment conducive to bone growth. Any imbalance in the formulation could hinder either the antibacterial or regenerative functions, which could impact the overall treatment outcome [45].

From the perspective of patient compliance, local drug delivery systems provide a streamlined approach. Once implanted, they offer continuous treatment at the infection site without requiring frequent dosing or patient intervention, as would be necessary with systemic antibiotics [44,46–48]. This minimizes patient burden and improves compliance by reducing the need for complex regimens. Nonetheless, these systems do require accurate surgical placement, which can be invasive. This invasiveness may pose a barrier for some patients, especially those for whom surgical procedures carry additional risks [44,46–49].

The administration complexity is also an important consideration. Local drug delivery systems, once placed, simplify post-operative care by eliminating the need for ongoing drug administration [50]. However, their placement typically involves precise surgical techniques and specialized skills, increasing the overall complexity of treatment. This complexity can also raise procedural costs and may limit accessibility in facilities where specialized equipment or expertise is not available [50,51].

In terms of therapy duration, local delivery systems are beneficial for providing prolonged, controlled antibiotic release at the infection site [45]. This sustained release reduces the need for frequent re-administration and is particularly valuable in treating chronic infections that require steady drug exposure over time. However, the fixed release profile means that adjusting or stopping treatment post-implantation is challenging. Should complications arise or a change in therapy become necessary, another invasive procedure would be required to remove or replace the implant, limiting the flexibility of this approach [45].

The use of biomaterials for local delivery also impacts the risk of infection. Once implanted, these systems generally reduce the need for ongoing invasive procedures, which may lower the overall risk of infection over time. However, the initial surgical placement of the delivery system introduces a risk, as any breach in sterility could result in infection at the implantation site [41,45]. Careful attention to sterile technique is essential during the procedure to mitigate this risk. Additionally, the implanted material itself may pose a risk of biofilm formation if not properly managed [41,45].

Monitoring and adjusting therapy with local delivery systems present further challenges. Once implanted, these systems provide consistent drug delivery, which can reduce the need for frequent monitoring [52]. However, this also means that dose adjustments are not readily possible. If the patient's response to treatment changes, modifications to the dosage or treatment strategy would require another surgical intervention, as dosage cannot be altered non-invasively. This inflexibility underscores the importance of careful pre-treatment planning to ensure optimal dosing from the outset [41,45,52].

Cost considerations are an important factor in the use of local drug delivery systems. While these systems may be cost-effective in the long run by reducing the need for repeated treatments or prolonged therapy, they often come with a high initial cost [53]. This is due to the expenses associated with surgical implantation, specialized biomaterials, and the technical skill required. Although these upfront costs may be offset by shorter hospital stays and fewer follow-up treatments, they can represent an initially significant financial burden [53].

In terms of invasiveness, local drug delivery systems minimize the need for further invasive procedures once they are in place [53]. This can enhance patient comfort and reduce the risk of complications associated with repeated interventions. However, their initial placement is an invasive surgical procedure, which introduces inherent risks such as infection, surgical complications, and longer recovery times. For some patients, particularly those with underlying health conditions, the invasiveness of these systems may be a notable drawback [53].

Another key advantage of local delivery systems is their efficacy in biofilm penetration [41,45,52,54,55]. High local antibiotic concentrations enable the effective disruption of

biofilms, ensuring sustained exposure that can overcome the biofilm's protective barriers. This capability makes local delivery particularly valuable in treating biofilm-associated infections like osteomyelitis [41,45,52]. However, if the drug release is not well-controlled, the concentration may not remain high enough over time to fully eradicate the biofilm, allowing biofilm-protected bacteria to survive and potentially cause recurrent infection [41,45,52].

Finally, the flexibility of treatment with local delivery systems is both an advantage and a limitation [52,53]. While these systems provide consistent, controlled drug release ideal for long-term stable dosing, the fixed dosage after implantation limits flexibility. Adjustments to the treatment are difficult or impossible without further surgery, as any changes to the drug regimen depend on the initial formulation. Side effect management is generally simplified by the reduced systemic exposure, minimizing common issues like gastrointestinal upset or nephrotoxicity. However, if side effects do occur, managing them can be challenging due to the fixed nature of the implant, which restricts the ability for immediate dosage adjustments [52,53].

3. Calcium Phosphate Bioceramic Systems for Treating Osteomyelitis

Innovative materials, particularly CaPs, are being engineered into various forms such as scaffolds, coatings, injectable pastes, and nano/microparticles to enable targeted delivery of therapeutic agents directly to infected bone areas. These systems can be loaded with antibiotics or other therapeutic agents, offering sustained and controlled release at the infection site, maximizing local drug concentration while minimizing systemic side effects. In addition to infection control, CaPs promote bone regeneration, making them highly effective for treating osteomyelitis, where both eradicating infection and facilitating bone repair are essential.

3.1. General Considerations

CaPs are ceramic material specifically engineered for medical applications, particularly bone tissue engineering and regenerative medicine. Their structure and composition make them exceptionally suitable for these uses due to their excellent biocompatibility, osteoconductivity, and mechanical properties.

CaPs are typically composed of chemically similar materials to bones' mineral components [56,57]. CaPs encompass a diverse range of CaPs characterized by their Ca/P molar ratio and specific compositions. Examples include amorphous calcium phosphates (Ca/P ratio: 1.2–2.2), α-tricalcium phosphate (Ca/P ratio: 1.5, which is rapidly resorbable), β-tricalcium phosphate (Ca/P ratio: 1.5, resorbing more slowly than the α form), and HA (Ca/P ratio: 1.67, generally non-resorbable except in nanometric form) [58]. Synthesis methods for nanosized HA with diverse structures [58]. Additionally, CaPs include calcium silicates such as tricalcium silicates and β-calcium silicates [59], bioactive glasses like silicate, borate, borosilicate, phosphate-doped, and mesoporous bioactive glasses [60], as well as bioactive glass ceramics, which are partially crystallized materials formed through the controlled nucleation and crystallization of glass [61]. CaP bioceramics have been successfully used in applications involving contact with soft tissues [62].

CaPs can be fabricated into various forms, including dense, porous, and composite structures. CaPs are particularly beneficial for bone regeneration as they facilitate cell infiltration, vascularization, and nutrient exchange, mimicking as close as possible the natural bone structure [63].

CaPs are inherently biocompatible, meaning they do not elicit a significant immune response when implanted in the body. This characteristic ensures the implant integrates well with the surrounding tissues and does not cause adverse reactions [64].

Osteoconductivity refers to a material's ability to serve as a scaffold for new bone growth. CaPs, specifically HA and tricalcium phosphate (TCP), are osteoconductive, providing a structure that supports the attachment and proliferation of osteoblasts, the cells responsible for bone formation [65].

CaPs possess excellent mechanical properties, such as high strength and toughness, making them ideal for load-bearing applications. Materials like alumina and zirconia are commonly used in hip and knee replacements due to their exceptional wear resistance and durability [66]. Additionally, certain CaPs, such as HA, are bioactive, meaning they can form direct bonds with bone tissue. This bioactivity is essential for ensuring the stable integration of implants with natural bone, enhancing both the stability and longevity of the implant [67]. Moreover, CaPs can function as effective drug delivery systems. Their porous structure enables the incorporation and controlled release of therapeutic agents, making them valuable for treating bone infections, promoting healing, or delivering chemotherapeutics to bone tumors [68].

3.2. Insights into the Mechanical Properties of Calcium Phosphate Bioceramics

CaPs are increasingly recognized for their potential in orthopedic applications, particularly for bone regeneration and repair, due to their bioactivity, osteoconductivity, and compatibility with biological tissues [62]. However, their applicability in load-bearing zones—such as the hip, knee, and spine—depends on their mechanical properties, which must withstand the physical demands imposed by daily activities and extended use [69].

CaPs possess inherent brittleness, which limits their fracture toughness and makes them less suitable for high-stress environments compared to metals or polymer composites. This brittleness can lead to fracture under impact or cyclic loading, posing a challenge for their use in areas subjected to repetitive stress [69]. Consequently, CaPs are most commonly applied in non-load-bearing or low-load-bearing implants, where their mechanical limitations are less impactful [69].

Although CaPs demonstrate strong bioactivity, they remain brittle with low fracture toughness, impact resistance, and tensile strength [70]. It is generally acknowledged that improving the bioactivity of CaPs often conflicts with enhancing their mechanical performance [71]. High sintering temperatures can increase their mechanical strength; however, the denser structure produced by this process can reduce bioactivity. Finding a balance between mechanical strength and bioactivity enhancement remains a critical research focus in tissue engineering. Extensive research has been conducted to improve the biological and mechanical characteristics of CaPs, aiming to advance their use in load-bearing applications and repair of segmental bone defects [71,72]. To date, there are limited comprehensive reviews addressing systematic enhancements to the mechanical properties of CaPs. However, the review by Li et al. seeks to fill this gap by summarizing both current and emerging research, focusing on strategies like fine-grain strengthening, second-phase reinforcement, sintering process optimization, and other advanced treatments [69].

To enhance the applicability of CaPs in load-bearing zones, researchers have also focused on developing composite materials that improve strength and wear resistance while retaining desirable bioactivity for bone implants.

Ceramic matrix composites are engineered with ceramic fibers or particulates embedded in a ceramic matrix, enhancing fracture toughness and wear resistance over monolithic ceramics. For example, incorporating reinforcing fibers such as carbon or silicon carbide increases the material's resistance to cracking and wear, making it suitable for high-stress areas like the hip and knee joints, as shown by Behera et al. [73]. Research incorporating multi-walled carbon nanotubes into HA composites has shown that this enhancement increases wear resistance by up to 20%, suitable for applications requiring both bioactivity and durability [74]. This composite combines HA, carbon nanofibers, and polycaprolactone to enhance adhesion strength and mechanical durability. The integration of carbon nanofibers improves scaffold elasticity, while HA provides bioactivity, creating a composite well-suited for reconstructive orthopedic applications. This scaffold has shown excellent potential for supporting bone regeneration in load-bearing sites, such as the femur and tibia [75].

Polymer–ceramic nanocomposites, such as polyetheretherketone–HA composites, combine CaP with polymers to achieve necessary mechanical strength for orthopedic

applications. Studies by Abu Bakar et al. demonstrate that these composites provide excellent fatigue resistance under tension, making them viable for long-term use in load-bearing scenarios [76]. In this composite, CaP particles are embedded within biopolymer matrices, allowing for enhanced bone regeneration while maintaining strength in weight-bearing areas. The biopolymer matrix degrades in conjunction with bone healing, leaving a gradually resorbing scaffold that supports osteointegration. This approach has shown promising results in large-segment bone repair, including long bones like the tibia and femur, where high load resistance is essential [77]

Further advancements involve magnesium-doped HA composites. Magnesium doping refines grain size, improving compressive strength and high-stress tolerance, making it a promising candidate for weight-bearing bone implants [78]. In another study, Yoshii et al. synthesized calcium phosphate/polyurethane composites with HA and β-TCP, enhancing cell viability and osteoconductivity in vivo, which are critical for load-bearing applications [79]. In this study, CaP composites were enriched with biominerals like magnesium, zinc, and strontium, which improved their bioresorbability and resemblance to the natural mineral composition of human bone. The addition of these trace elements enhances bone integration and cell viability, while the nanocrystalline CaP forms a stronger bond within a polycaprolactone matrix. This composite is especially promising for load-bearing applications due to its accelerated bioresorption rate and enhanced mechanical properties [80].

HA–titania (HA-TiO_2) nanocomposites, as reported by Salarian et al., significantly improved compressive and flexural strength, highlighting their potential in bone tissue engineering [81]. Additionally, biomimetic HA/bioactive glass composites achieved enhanced fracture toughness and tensile strength, suitable for load-bearing implants, as studied by Bellucci et al. [82]. A combination of HA and polyethylene, forming HA–polyethylene composites, further improved mechanical performance, mimicking natural bone structure [83].

Other promising composites include calcium silicate-reinforced HA, which has flexure strength closely resembling mineral bone, making it suitable for high-stress applications [84]. HA/polycaprolactone-coated biphasic calcium phosphate (BCP) scaffolds demonstrated significant improvement in mechanical strength and osteogenic differentiation, highlighting their application in load-bearing scenarios [85].

Lastly, collagen-integrated HA cement provided a 10-fold increase in toughness, making it appropriate for moderate load-bearing applications as shown in studies by Moreau et al. [86].

These studies collectively illustrate the advancements in composite formulations for CaP, allowing for expanded use in load-bearing orthopedic implants. Through innovations in fiber reinforcement, polymer–ceramic combinations, and doping techniques, researchers are overcoming the inherent brittleness and wear limitations of CaPs, creating materials that are both mechanically robust and bioactive.

3.3. Calcium Phosphates

CaPs are minerals composed of calcium cations and phosphate anions, serving as the primary inorganic component of roughly 60% of human bone tissue [87]. However, the performance of different CaPs varies significantly. Some types degrade slowly in vivo, while others exhibit reduced stability; certain forms are osteoinductive, whereas others are not [42]. Predominantly, there are three types of CaP: HA-$Ca_{10}(OH)_2(PO_4)_6$), tricalcium phosphates (TCP, $Ca_3(PO_4)_2$), and BCP [88]. The latter is a combination of HA and TCP in varying weight ratios, chosen to achieve an optimal balance between the more stable HA phase and the more soluble TCP phase.

3.3.1. HA in the Context of Osteomyelitis

fHA is widely recognized for its beneficial role in bone-related applications due to its biocompatibility and osteoconductive properties. The preparation techniques of HA

is extensively documented in the literature [43,89–95]. In the context of osteomyelitis, HA serves multiple purposes: it integrates seamlessly with bone tissue, promotes bone regeneration, and can be functionalized with antibacterial agents for localized drug delivery to combat infection. The use of HA scaffolds, coatings, and composites has shown great promise in addressing the dual challenges of bone regeneration and infection management in osteomyelitis.

As mentioned above, the treatment of osteomyelitis presents the dual challenge of eradicating infection and simultaneously promoting bone healing.

One promising approach involves functionalizing HA with antibacterial agents. These agents, including natural compounds like berberine and Cs, or metal ions such as silver (Ag), zinc (Zn), strontium (Sr), and copper (Cu) can be incorporated into HA to create a localized delivery system that gradually releases antibacterial agents at the infection site [96–98]. This targeted delivery system not only fights bacterial pathogens but also minimizes systemic side effects while stimulating bone regeneration.

For instance, the development of Ag nanoparticle-decorated HA (HAp/AgNPs) nanocomposites has demonstrated strong antibacterial activity against *S. aureus*, with the efficiency being influenced by the amount and size of the deposited AgNPs [97]. Another study synthesized Ag/Sr co-substituted HA (Ag/Sr-HA) nanoparticles, which exhibited excellent antibacterial activity against *E. coli* and *S. aureus* [98]. Additionally, Sr substitution was found to enhance cell proliferation and differentiation, upregulate osteogenic gene expression, and induce cellular mineralization of cells. Interestingly, Sr substitution in Ag/Sr-HA nanoparticles mitigates the negative effects of Ag enhancing the biological activity of HA. Despite these promising in vitro results, translating these approaches into in vivo models and conducting more extensive clinical trials are essential to fully evaluate their real potential therapeutic impact on patients with osteomyelitis [98].

In addition, HA scaffolds not only provide structural support for bone regeneration but also serve as an effective vehicle for delivering antibacterial agents, enabling simultaneous infection control and bone healing. By incorporating antibiotics or metal ions such as silver or zinc into the HA matrix, the scaffold can gradually release these agents, targeting bacterial infections while promoting osteogenesis. This dual functionality is crucial in osteomyelitis treatment, where both the eradication of infection and the regeneration of bone tissue are essential for successful recovery. Moreover, the controlled degradation of HA provides a sustained release of therapeutic agents, ensuring long-term protection against infection while encouraging new bone formation in the affected area.

Zhan et al. developed a scaffold material incorporating microspheres to create a dual sustained-release system using Cs and nano-HA (Cs-HA) as a carrier for Bone Morphogenetic Protein-2 (BMP-2) and VAN. BMP-2 and VAN-loaded microspheres were prepared via an emulsion ultrasonic method, and the composite was characterized for surface structure, compressive strength, porosity, and biodegradation. Scanning electron microscope (SEM) images confirmed a uniform porous and rough surface with enhanced thermal stability, achieving a high compressive strength of 1.912 ± 0.012 KPa. The BMP-2 loading rate was $59.61 \times 10^{-4} \pm 0.023 \times 10^{-4}$% with an encapsulation efficiency of 6.022 ± 0.005%. The release rates of VAN and BMP-2 were 57.194% and 12.968%, respectively. The osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) was verified by alkaline phosphatase quantification and the mineralization of the extracellular matrix, as indicated by calcium phosphate deposition detected by Alizarin Red staining. The Cs-HA hydrogel demonstrated sequential dual-drug release, supporting bone regeneration by sustaining growth factors and antibiotics delivery. Over a 31-day observation, the hydrogel retained drug particles, maintained a 55% degradation rate, and provided structural support for bone regeneration. With a controlled gel-forming speed of about 2 min, the hydrogel showed stable thermal properties and enabled sustained release for over 30 days, with a projected total release period of 50 days. No negative effects on cell viability were observed over 72 h, supporting the system's biocompatibility. Further research will build on these findings [99].

Similarly, a study from Mulazzi et al. evaluated the effectiveness of bone-hybrid scaffolds composed of type I collagen (Coll) and magnesium-doped HA (MgHA) for local drug delivery to prevent bone infections [100]. The scaffolds were loaded with VAN hydrochloride and gentamicin sulfate to assess their capacity for controlled antibiotic release. The study found that MgHA/Coll scaffolds can effectively bind and release antibiotics, with drug retention and release influenced by the amount of MgHA present. Scaffolds containing 70 wt% MgHA demonstrated slower drug release due to greater drug binding (Figure 3). Interestingly, the antibiotics released from the scaffolds retained their full antibacterial activity against both Gram-positive and Gram-negative bacteria. These findings suggest that MgHA/Coll scaffolds, loaded with antibiotics, offer a promising approach for infection control during bone surgery without compromising biocompatibility or regenerative potential.

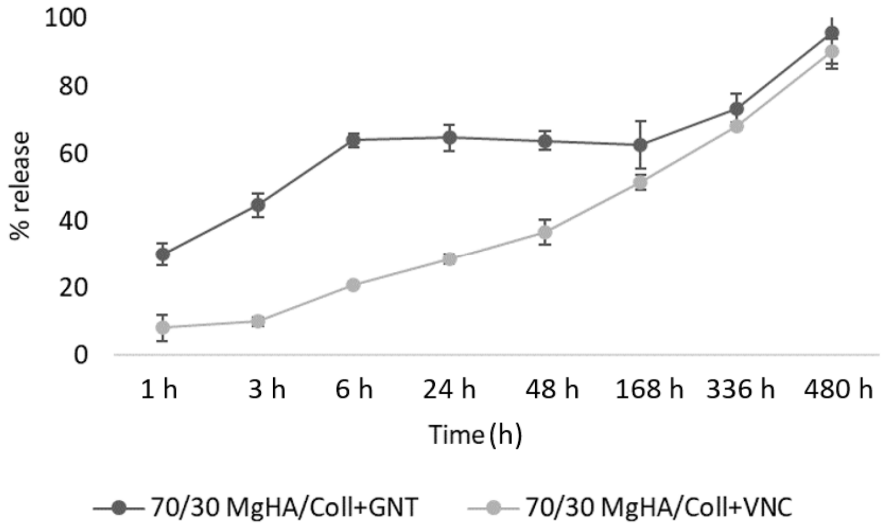

Figure 3. Comparison of the release profiles for VAN hydrochloride and gentamicin sulfate, reproduced from [100], MDPI, 2011.

In another study, the porous composite microspheres made of HA, di-calcium phosphate di-hydrate (DCPD), and Cs (here, referred as Chi) were successfully prepared via the hydrothermal method. Cs served as a chelating agent, promoting the growth of CaPs. These composite microspheres exhibit a specific surface area of 38.16 m^2/g and a pore volume of 0.24 cm^3/g, with pore sizes between 4 and 100 nm, making them potential pharmaceutical carriers due to Cs properties and the structure's high porosity. Upon annealing, Cs condensed and DCPD transformed into $Ca_2P_2O_7$ at 300 °C. At 500 °C, $Ca_2P_2O_7$ combines with HA to form β-TCP, with Cs fully combusted, resulting in microspheres composed of $Ca_2P_2O_7$, β-TCP, and HA. These characteristics make them suitable as injectable bone graft materials. Characterizations confirmed the composition of 54.2 wt% HA, 29.8 wt% DCPD, and 16 wt% Cs. In vitro drug release tests with gentamicin, vancomycin, and zyvox followed a three-phase release profile: an initial burst within 24 h, a steady release from days two to seven, and a slower release rate from weeks two to three. With their high pore volume and specific surface area, these microspheres demonstrate strong potential as drug carriers (Figure 4) [101].

A recent study has examined the properties and drug release capabilities of antibiotic-loaded apatite cement (AC) and alpha-tricalcium phosphate (α-TCP) AC/α-TCP composites. In this context, gentamicin-loaded AC/α-TCP composites were prepared with two mixing ratios (10:3 and 10:6), creating a cement paste molded and cured under controlled conditions for 24 h. Notably, gentamicin release from these composites maintained a concentration above the minimum inhibitory level for *S. aureus* for up to 30 days in both mixing ratios, highlighting the potential of gentamicin-loaded AC/α-TCP composites as an effective localized drug delivery system (Figure 5) [102].

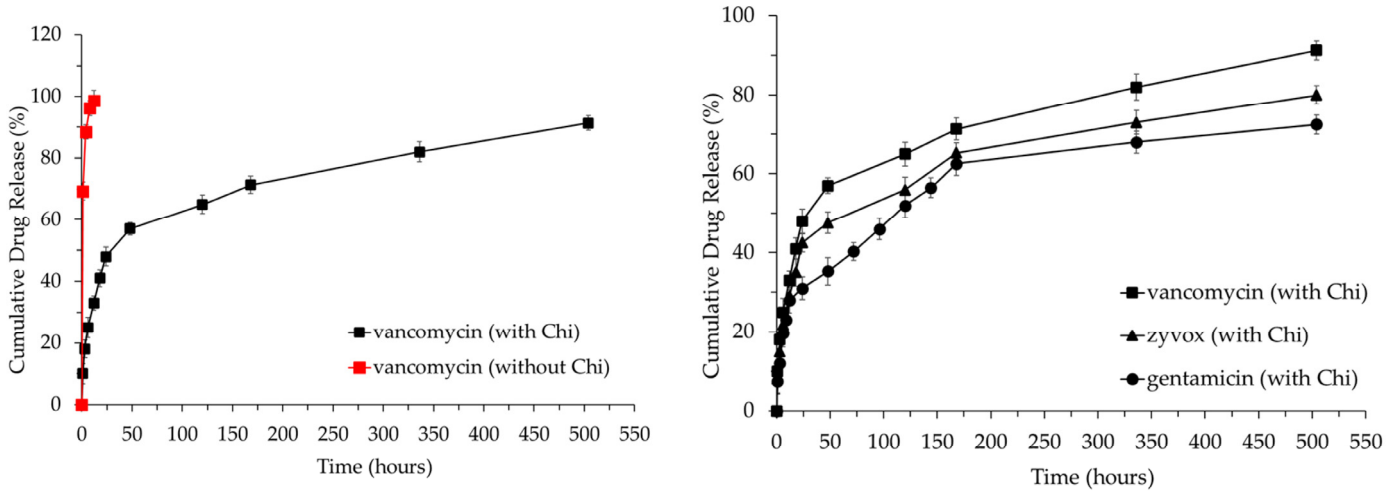

Figure 4. The cumulative drug release profile shows (**a**) V-Chi-CaPM with (black) and without (red) additional Cs, and the (**b**) VAN–Chi-CaP microsphere; the zyvox–Chi-CaP microsphere; and the gentamicin–Chi-CaP microsphere formulations with additional Cs. Reproduced from [101], MDPI, 2024.

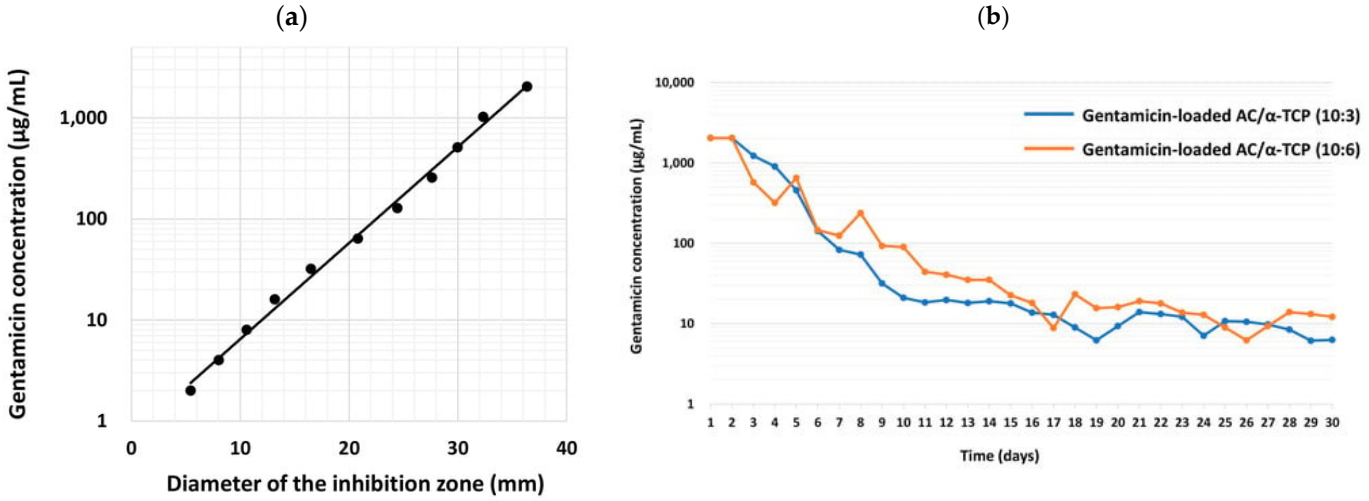

Figure 5. (**a**) Relationship between gentamicin concentrations and the diameters of the inhibition zone in an agar plate coated with *Staphylococcus aureus*; (**b**) The concentration of gentamicin released from gentamicin-loaded AC/α-TCP composites. Reproduced from [102], MDPI, 2023.

Modifying the surface properties of different medical devices with HA mixtures/complexes represents another direction for the localized treatment of osteomyelitis [103]. These surface modifications help to preserve the efficacy of antibacterial treatments and minimize the risk of recurrent infections. There are two primary strategies for activating an implant surface: modifying (a) the surface chemistry and (b) the surface topography at macro-, micro-, and nanoscale levels. Implant-based coatings can address both strategies by altering both the chemical composition and the morphology of the implant surface.

Moreover, CaPs can serve as highly effective drug delivery systems. Their porous structure allows for the incorporation and controlled release of therapeutic agents, which makes them particularly useful for treating bone infections, enhancing tissue regeneration, and delivering targeted chemotherapeutics to bone tumors.

In this sense, a study investigated the effects of Ag-containing HA (Ag-HA) VAN on MRSA biofilm formation in prosthetic joint infections. Ag-HA-coated disks showed

reduced biofilm formation and bacterial counts compared to HA-coated and titanium disks. The combination of Ag-HA with VAN was the most effective in reducing MRSA biofilms. These findings suggest that Ag-HA with VAN could be a promising strategy for preventing and treating [104].

In this study, zinc-doped HA (Zn-HA) was successfully synthesized using the co-precipitation method, resulting in grain sizes between 50 and 200 nm. At a zinc doping concentration of 0.05 M (Zn3), the material exhibited strong antibacterial properties and maintained the stable HA phase, avoiding the formation of the calcium zinc phosphate phase. For application as a coating on Ti-6Al-4V alloy, 0.05 M Zn-HA was applied via flame spraying to create a Zn-HA layer. Qualitative and quantitative antibacterial tests showed a significant inhibition zone, with the persistent release of Zn ions enhancing antibacterial effectiveness over time. After 3 h, the antibacterial rate reached 99.9%, demonstrating potential for osteomyelitis treatment. Biocompatibility assessments using the WST-1 cell activity assay and lactate dehydrogenase (LDH) cytotoxicity assay showed normal cell growth and no cytotoxic effects, highlighting the excellent biocompatibility of the Zn-HA coating for osteomyelitis applications [105].

Another study focuses on the synthesis, characterization, and antibacterial properties of zinc and iron-doped HA (ZFHA) for osteomyelitis treatment. Using a response surface methodology with central composite design in design expert software, process parameters were optimized. Analyses confirmed the presence of calcium iron hydrogen phosphate and Parascholzite as primary phases, with optimal conditions determined to be 0.09 M Zn and 0.04 M Fe at 65 °C, yielding 71.29% calcium iron hydrogen phosphate and 28.71% Parascholzite phases. The resulting nanopowder exhibited a mixed morphology of spherical and rod-shaped particles, characteristic of its biphasic composition. The ZFHA sample demonstrated broad-spectrum antibacterial activity, with IC50 values of 4.02 mg/mL against *E. coli* and 4.79 mg/mL against *S. aureus*. It also showed high biocompatibility with osteoblast-like MG-63 cells, enhancing biomineralization. These antibacterial and osteoinductive properties of the Fe and Zn-doped HA suggest its promising application for osteomyelitis-related treatments [106].

Carbonate apatite honeycomb scaffolds were functionalized with Cu via a dissolution–precipitation reaction. The scaffolds maintained their honeycomb structure after immersion in $CuCl_2$ solution, where Cu was precipitated as libethenite [$Cu_2(OH)PO_4$] on the surface. Surface Cu concentration was controlled by the $CuCl_2$ solution concentration. Scaffolds with 23.8 wt% Cu showed both antibacterial and cytotoxic effects, while those with $\leq$4.6 wt% Cu demonstrated antibacterial activity without impairing osteoblast-like cell adhesion, proliferation, differentiation, or calcification. Scaffolds with 4.6 wt% Cu successfully inhibited bacterial growth for at least 28 days and promoted angiogenic and osteogenic effects in vivo. These findings support the potential use of Cu-functionalized scaffolds as an innovative therapy for osteomyelitis [107].

In another report, the authors developed a composite of Ag and tannin-modified HA (Ag-THA) with polyurethane (PU) and evaluated its antimicrobial and bone-regenerative properties in a rat femoral defect model. The PU/Ag-THA composite showed strong in vivo antibacterial activity, reducing bacterial presence to below 3% at 12 weeks post-operation. Additionally, it significantly improved bone mineral density and osteoinductivity compared to controls. These findings highlight the potential of Ag-THA as an effective, scalable material for antimicrobial orthopedic implants [108].

Another in vivo study evaluated the biomechanical, histomorphometric, and histological performance of nanostructured HA (HAnano) coatings compared to dual acid-etched (DAA) surfaces on implants in sheep. The in vivo osseointegration evaluation of implants coated with nanostructured HA in low density bone [109]. Ten sheep received 20 implants, and the surfaces were analyzed using microscopy and spectroscopy. Both groups showed increased bone-implant contact and bone area fraction occupancy over time. However, after 28 days, the HAnano-coated implants demonstrated significantly superior bone-implant

contact and bone area fraction occupancy values compared to the DAA surfaces, suggesting that HAnano coatings enhance bone formation in low-density bone.

In addition, the antibacterial properties and biocompatibility of TiO_2 nanotubes loaded with HA and gentamicin were also investigated [110]. In vitro tests demonstrated improved cell compatibility and extended gentamicin release (up to 22 days) compared to standard coatings. Translating to in vivo models, rats implanted with gentamicin-loaded HA/TiO_2 nanotubes showed no infection, unlike control groups (Figure 6). The findings suggest that gentamicin-HA-TiO_2 nanotubes offer a promising prophylactic approach against prosthetic infections, outperforming standard titanium implants.

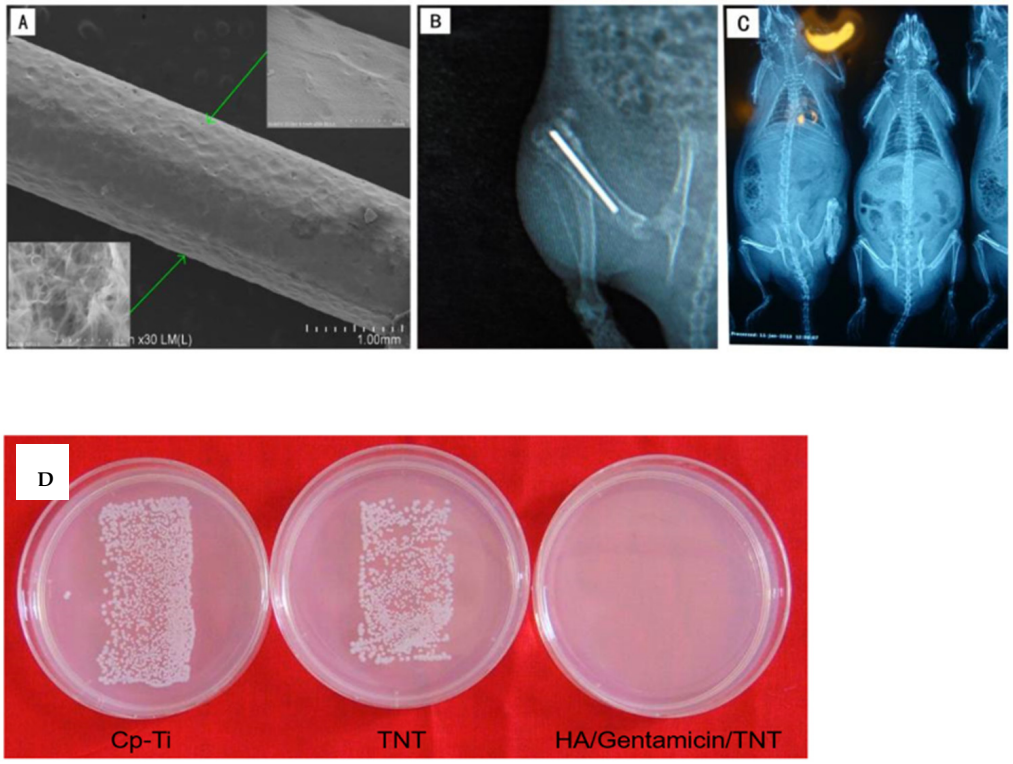

Figure 6. Surgical procedure and in vivo antibacterial efficacy. (**A**) Overview of the surgical procedure. (**A**) Depiction of HA/gentamicin/titanium nanotube (TNT) rods. (**B**, **C**) Postoperative X-rays showing the implanted titanium rods within the tibia of the rat model. (**B**) Antibacterial efficacy evaluation. The bare Ti group exhibited a 100% infection rate, while the TNT group had a 92% infection rate. In contrast, the HA/gentamicin/TNT group showed a 0% infection rate, demonstrating a significantly reduced infection rate compared to both the bare Ti and TNT groups. (**D**) The bare Ti group exhibited an infection rate of 100%, while the TNT group showed a slightly lower rate of 92%. In contrast, the HA/gentamicin/TNT group demonstrated a 0% infection rate, representing a significant reduction in infection compared to both the TNT and bare Ti groups. Reproduced from [110], MDPI, 2021.

In a recent research article, the team developed a Ti alloy coated with simvastatin and HA (Sim-HA) using electrochemical deposition. The Sim-HA coatings demonstrated significant inhibition of *S. aureus* biofilm formation and enhanced the biocompatibility of the titanium alloy. In vivo studies in rat femurs confirmed that Sim-HA coatings effectively prevented *S. aureus*-induced implant-associated infections, as evidenced by radiological and histological assessments. The antibacterial properties of the Sim-HA coatings were linked to their ability to inhibit biofilm formation, as observed through scanning electron microscopy and bacterial spread plate analysis. Additionally, Sim-HA coatings promoted osteogenesis and osteointegration, as validated by micro-computed tomography (μCT), histological analysis, and biomechanical pull-out tests. Overall, Sim-HA coatings represent a promising strategy for protecting implants against biofilm-associated infections [111].

In osteomyelitis, infected and necrotic bone tissue often needs to be removed, leaving defects that require reconstruction. These bone voids require a scaffold that can provide structural support while also promoting the regeneration of healthy bone tissue. HA can fill these bone defects, providing structural support and promoting the formation of new bone [112]. As HA gradually dissolves, it releases calcium and phosphate ions, which are essential for the mineralization process in bone healing.

A novel injectable formulation combining an osteoconductive polyelectrolyte complex (PEC) and HA for controlled ciprofloxacin delivery has been developed for osteomyelitis treatment. This system uses a biodegradable PEC derived from Cs, complexed with ciprofloxacin-loaded nascent hydroxyapatite (n-HA). Characterization through FT-IR, XRD, TGA, and TEM confirmed PEC's structural and functional properties, combining the crystallinity and osteoconductivity of n-HAP with the controlled degradation and hydrophilicity of the PEC network. Cytocompatibility was demonstrated via MTT assays and cytoskeleton staining in MG-63 cells, with early biomimetic mineralization observed under simulated physiological conditions, reaching Ca/P ratios of 1.23 on day 3 and 1.55 on day 6. Alizarin Red S staining and calcium quantification validated successful biomineralization in MG-63 and HOS cells within a week. Antibacterial efficacy was confirmed by ciprofloxacin release kinetics and disk diffusion tests against *S. aureus* and *E. coli*. This injectable PEC system, featuring osteoconduction, early biomineralization, and antibacterial activity, shows strong potential for osteomyelitis treatment due to its biodegradability and multifunctional capabilities [113].

A novel study presents a viable alternative to autografts using a porous HA scaffold, evaluated in both infected and non-infected scenarios, with or without antibiotic treatment. In an experimental model involving twenty-four New Zealand white rabbits, a critical-sized defect in the femur was surgically created and treated with either an HA scaffold or pulverized bone autograft (PBA) [114]. The two graft types were assessed in both septic and aseptic conditions, with or without antibiotic intervention. HA scaffolds were characterized using μCT, and following euthanasia, μCT, histological analysis, and white blood cell component analysis were performed. The results revealed that HA scaffolds achieved significantly greater mineralization relative to total volume compared to PBA, with values of 27.56% for HA and 14.88% for PBA ($p < 0.001$). Additionally, the HA scaffolds in the septic groups exhibited significantly greater mineralization than the aseptic groups, irrespective of antibiotic use ($p = 0.016$). Furthermore, bone quality, as indicated by bone mineral density, was significantly higher in the HA groups (67.01 ± 0.38 mgHA/cm^3) compared to the PBA groups (64.66 ± 0.85 mgHA/cm^3) ($p < 0.001$). These findings suggest that HA scaffolds serve as a promising alternative to bone autografts for critical-sized defects, offering superior bone quality and quantity both in the presence and absence of infection [114].

Furthermore, porous scaffolds fabricated using a combination of HA and berberine via direct extrusion 3D printing have shown both regenerative properties and antibacterial effects against *S. aureus* [96]. Different formulations of HA, such as those combined with TCP to form biphasic calcium phosphates, offer customizable degradation rates [115]. This is particularly useful in treating osteomyelitis, where the balance between providing immediate structural support and allowing gradual bone regeneration is crucial.

3.3.2. Other Calcium Phosphates-Based Delivery Systems

Mixtures of different CaP phases, such as TCP and BCP are utilized to tailor the degradation rate and biological response. In this line, TCP has garnered significant attention in the treatment of bone infections due to its biocompatibility, bioactivity, and absorptive property [116,117]. Although TCP itself does not possess inherent antibacterial properties, it has been functionalized with various antibiotics (e.g., vancomycin, tobramycin, tetracycline, and gentamicin) or combined with metals or other materials to enhance its efficacy against bone infections [118–120]. In fact, the incorporation of antimicrobial agents into TCP scaffolds allows the localized delivery of these agents directly to the infection site, helping

to target bacterial pathogens while protecting against biofilm formation. For instance, TCP loaded with antibiotics such as gentamicin has been used to effectively treat osteomyelitis by releasing the antibiotic in a controlled manner over time [118].

Another key advantage of TCP is its absorptive property [116]. Over time, TCP degrades in the body and is replaced by new bone tissue, thereby eliminating the need for a second surgery to remove the implant. This resorption process is beneficial in the treatment of osteomyelitis, as it allows the gradual and replacement of the infected bone tissue by healthy bone tissue. Additionally, the degradation products of TCP are non-toxic and are safely metabolized by the body. For these reasons, TCP has been utilized in various clinical settings for the treatment of bone infections, particularly in cases of osteomyelitis. It is used as a bone graft substitute or as part of composite materials in bone void fillers, spacers, or scaffolds [117]. In all cases, both in vivo and clinical studies have shown promising results in terms of both infection control and bone healing [120,121].

For example, teicoplanin-loaded hydrogel formulations based on poloxamer 407 and undoped or Mg/Zn-doped TCP were developed. In vitro tests demonstrated biocompatibility, enhanced cell migration, osteogenic differentiation, and strong bactericidal effects comparable to standard osteomyelitis antibiotics. When translated to in vivo model, the teicoplanin-loaded formulations effectively treated osteomyelitis in rat tibias, outperforming teicoplanin-free formulations and parenteral administration [122].

In another study, the effectiveness of an antibiotic-loaded absorbable calcium sulfate/calcium phosphate (CS/CaP) composite as a bone substitute for treating chronic osteomyelitis, compared to CS alone was investigated. A retrospective review of 31 patients with chronic osteomyelitis was conducted. Group A (21 patients) received CS/CaP, while Group B (10 patients) received CS. The treatment involved debridement, antibiotic-loaded bone substitutes, systemic antibiotics, and multidisciplinary care. Bone formation and resorption were assessed through X-ray and μCT, while infection control was evaluated via lab tests and wound healing. The follow-up period averaged 61.3 weeks in Group A and 86.7 weeks in Group B. No patients in Group A had recurrent infections at 17 months, while two patients in Group B experienced recurrence. New bone formation was significantly higher in Group A at 1, 3, and 6 months (p = 0.001, p = 0.025, p = 0.000). Resorption rates were slower in Group A (p = 0.000 at all-time points), and infection recurrence rates differed significantly (p = 0.034). These results suggest that the antibiotic-loaded CS/CaP composite is a superior bone substitute compared to CS, with improved bone regeneration and a lower risk of infection recurrence in the treatment of chronic osteomyelitis [123]. Similarly, another study developed a novel local antimicrobial delivery system for treating osteomyelitis by incorporating Ag and ε-Polylysine into β-TCP beads. The incorporation of PL into the delivery system enhanced the antimicrobial efficacy of Ag-loaded systems through synergistic antibacterial action, while also serving as a nutrient source to promote bone regeneration. The porous structure of β-TCP beads increased the loading capacity for antimicrobial agents and supported bone regeneration [124]. This local antimicrobial material delivery system offers a comprehensive solution for treating various bone infections, including acute, chronic, debrided necrotic bone, and polymicrobial infections, by combining antimicrobial efficacy with osteoconductive properties for bone repair.

In a recent study, the authors developed an injectable drug delivery system using a poloxamer 407 hydrogel containing undoped and Mg, Zn-doped TCP along with teicoplanin, a broad-spectrum antibiotic. The study assessed the effects of teicoplanin and β-TCP addition on the hydrogel's micellization, gelation, particle size, and surface charge, followed by the evaluations of hydrogel degradation and drug release kinetics. In vitro studies examined bactericidal, biocompatibility, and osteogenic properties, and these findings were confirmed in vivo using Wistar rat models. Results showed that teicoplanin was encapsulated within the hydrogel micelle corona, resulting in an increased hydrodynamic radius and enabling sustained release throughout the study period. This release profile effectively conferred antibacterial activity against Gram-positive bacteria. The formulations demonstrated biocompatibility, bone healing, and osteogenic potential. In vivo

experiments further verified that local hydrogel injections yielded better osteomyelitis treatment outcomes and enhanced bone regeneration compared to parenteral administration. These formulations represent promising injectable drug delivery systems for osteomyelitis treatment and warrant further technological refinement [122].

For instance, a well-designed study evaluated a bioresorbable CaP scaffold for sustained antimicrobial drug release by assessing its efficacy in a murine model of femoral implant-associated osteomyelitis. The scaffold, incorporating rifampin and sitafloxacin—antibiotics effective against persistent bacterial phenotypes—was 3D-printed and coated with poly(lactic co-glycolic) acid (PLGA) to achieve controlled drug release over two weeks. When implanted in the murine infection model, the 3D-printed CaP scaffold showed significantly reduced bacterial colonization at 3 and 10 weeks post revision compared to gentamicin-laden polymethylmethacrylate (PMMA). Additionally, there was a marked increase in bone formation for the CaP scaffold loaded with rifampin at both time points. These findings demonstrate that osteoconductive, antimicrobial-loaded 3D-printed CaP scaffold provides superior bacterial colonization control and bone regeneration in a single-stage revision surgery (Figure 7), outperforming gentamicin-laden PMMA, which typically requires a two-stage revision [125].

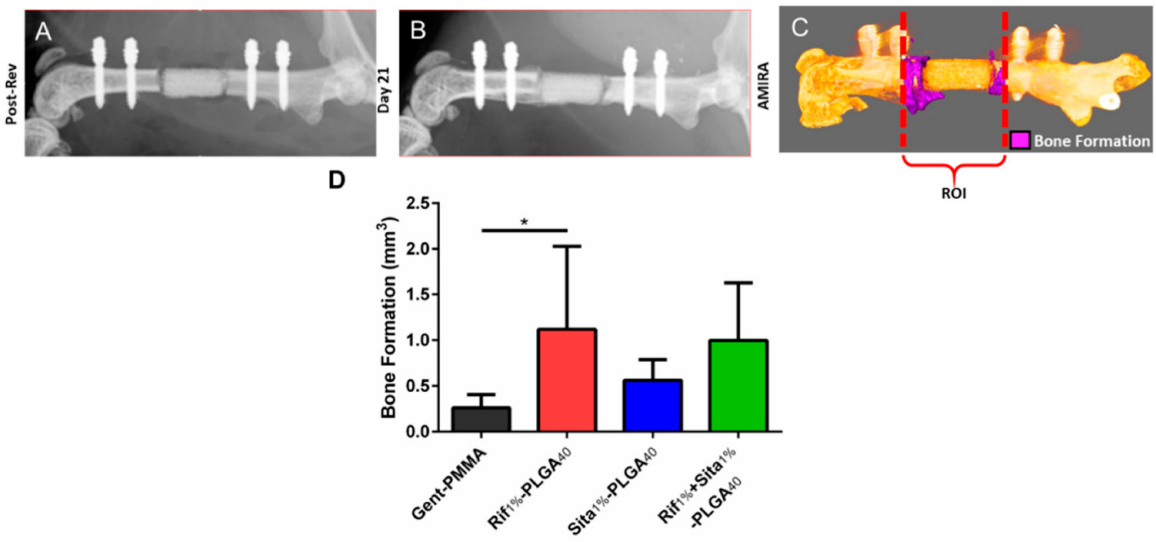

Figure 7. Bone formation following one-stage revision surgery was compared between gentamicin-impregnated PMMA cement spacers (Gent-PMMA) and a 3D-printed CaP scaffold loaded with rifampin (Rif1%-PLGA40), sitafloxacin (Sita1%-PLGA40), and a combination of both (Rif1% + Sita1%-PLGA40). (**A**,**B**) Bone formation was evaluated through µ-CT scans taken immediately post revision and 21 days later, prior to euthanasia. (**C**) Bone formation was quantified using digital registration and an overlay subtraction algorithm within the AMIRA software. (**D**) A significant increase in bone formation was observed for the Rif1%-PLGA40 group compared to the clinical control of Gent-PMMA (n = 4–7/group). * indicates statistical significance ($p < 0.05$) as determined by Dunnett's post hoc test following ANOVA. Data are presented as mean ± standard deviation. Reproduced from [125], MDPI, 2019.

Recent research has utilized low-temperature 3D-printing to fabricate PLGA/β-CaP/LL-37 antimicrobial peptide (PLGA/TCP/LL-37, PTL) scaffolds for the treatment of infected segmental bone defects. These scaffolds were produced in three variations: a high LL-37 concentration group (PTHL), a low LL-37 concentration group (PTLL), and a blank control group (PT). In vitro testing confirmed that the PTL scaffolds possess a porous structure conducive to the sustained release of LL-37, supporting its antimicrobial action over time. The PTHL group demonstrated significant antibacterial activity against *S. aureus* and *Escherichia coli* without affecting the proliferation or alkaline phosphatase activity of rat BMSCs. In a rat model with infected femoral bone defects, the PTHL scaffolds promoted

new bone formation within four weeks and eradicated bacterial presence, performing comparably to a VAN and cancellous bone mixture (Figure 8) [126].

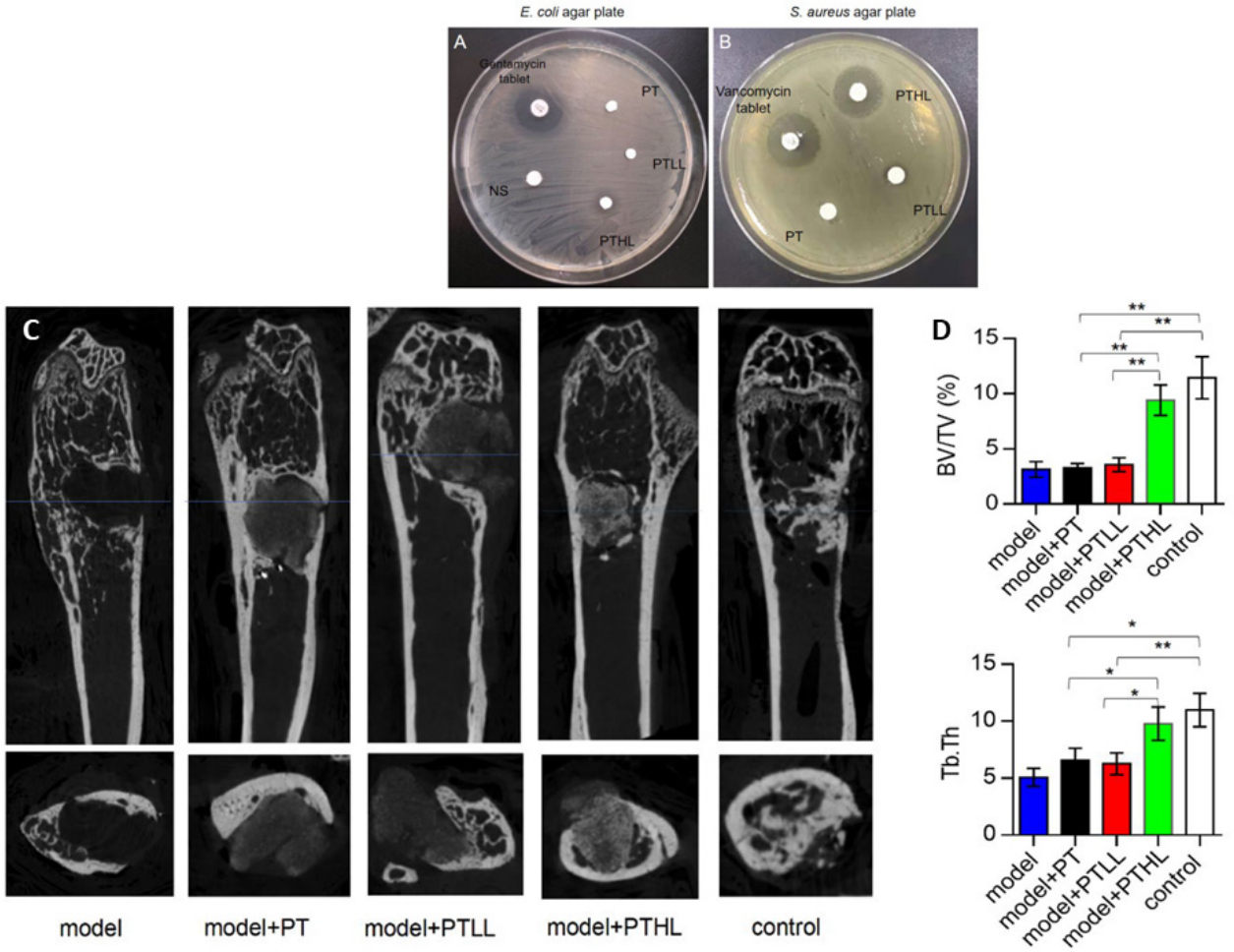

Figure 8. In vitro antibacterial testing of the PLGA/TCP/LL-37 grafts was conducted using *Escherichia coli* (**A**) and *S. aureus* (**B**) on agar plates. Positive controls included gentamicin and VAN tablets, while a blank PLGA/β-TCP group (PT) served as a comparison. The experimental groups were categorized as follows: PTLL (PLGA/β-TCP with low LL-37 concentration), PTHL (PLGA/β-TCP with high LL-37 concentration), and NS (normal saline tablet, used as a negative control). (**C**) Micro-CT imaging was performed to analyze *S. aureus*-infected femoral segmental defects in mice implanted with various scaffolds. Representative images were obtained in both coronal and horizontal planes for each group, providing visual insights into new bone formation. (**D**) Quantitative assessments included the bone volume fraction (BV/TV, expressed as the percentage of mineralized bone volume per unit sample volume) and trabecular thickness (Tb.Th, measuring the thickness of cancellous bone structures). The analysis revealed significant differences, with Student's t-test indicating statistical significance at * $p < 0.05$ and ** $p < 0.01$ for comparisons, represented as mean ± standard deviation (sd). Reproduced from [126], MDPI, 2023.

This study aimed to create fibroblast growth factor (FGF)-2-apatite composite layers on Ti pins in a single step at 25 °C using a supersaturated CaP solution and to compare their properties with layers formed at 37 °C. Ti pins were coated with varying FGF-2 concentrations (0.5, 1.0, 2.0 μg/mL at 25 °C for 24 h, and 4.0 μg/mL at 37 °C for 48 h). The composite layers showed similar mitogenic activity and chemical composition across methods, with the Ca/P molar ratio being significantly lower at 25 °C, suggesting less mature apatite or more amorphous calcium phosphate. In vivo results indicated lower pin tract infection and osteomyelitis rates for 37 °C samples containing 4.0 μg/mL FGF-2 at

37 °C for 48 h (37F4.0) compared to 25 °C samples containing 0.5, 1.0, or 2.0 µg/mL FGF-2 at 25 °C for 24 h. The extraction torque for 37F4.0 was also higher, indicating stronger fixation (0.276 Nm vs. 0.192–0.176 Nm, $p < 0.05$). Additionally, *S. aureus* invasion was significantly lower for 37F4.0. Overall, the composite formed at 25 °C was less effective in enhancing fixation strength and infection resistance, suggesting that the CaP matrix's chemistry, along with FGF-2 content and activity, critically influences infection resistance and mechanical stability [127].

Liu et al. developed calcium phosphate cement (CaPC) systems designed for controlled release of the antibiotic doxycycline, achieved by adjusting the formulation. Key components included hydrolytically degrading PLGA particles, varying doxycycline concentrations, and the addition of the lubricant carboxymethyl cellulose. The resulting CaPC formulations demonstrated favorable handling characteristics, including suitable injectability and setting times. Doxycycline release from the CaPCs followed a controlled profile, characterized by an initial burst release and a cumulative release reaching 100% over eight weeks. The antibiotic retained its effectiveness against *S. aureus*, a primary pathogen in osteomyelitis. An in vivo implantation model confirmed the CaPC's antibacterial efficacy, showing a rapid reduction in *S. aureus* populations both at the CaPC surface and in adjacent tissues [128].

A comparative study examined the bacterial and osteoblastic cell responses to two nanoparticulate carriers of clindamycin. The carriers included a pure calcium phosphate composition and a PLGA-coated CaP formulation. Three non-cytotoxic phases of calcium phosphate with varying drug release durations (from one week up to a year) were utilized: monetite, amorphous calcium phosphate, and hydroxyapatite. The clindamycin-loaded particles displayed sustained drug release, determined by the degradation rate of the carrier. All formulations exhibited effective antibacterial activity against *S. aureus* in both broth cultures and blood agar plates. Importantly, no cytotoxicity was observed in osteoblastic MC3T3-E1 cells over a three-week incubation period. The cells adhered closely to the antibiotic particles, regardless of the carrier's phase composition or coating. Additionally, the particles stimulated osteogenesis by upregulating key osteogenic markers—osteocalcin, osteopontin, Runx2, and protocollagen type I—demonstrating their potential to enhance bone regeneration at infected sites while addressing bacterial infections effectively [129].

Radwan et al. prepared composites using an in situ precipitation technique and loaded with moxifloxacin hydrochloride (MOX). The resulting Cs-CaP composite scaffold (NP2-MOX) maintained stable CaP formation even with increased Cs content. The scaffold with the highest Cs content demonstrated good cell viability in MG-63 osteoblast-like cells. In animal models of osteomyelitis, the NP2-MOX scaffold effectively reduced bacterial load, inflammation, and bone necrosis, showing promise as a preventive platform for post-operative osteomyelitis. Additionally, the composite achieved complete drug release within three days and encouraged osteoblast differentiation and proliferation. These outcomes, including reductions in bacterial count, inflammation, and fibrosis in osteomyelitis-induced bone tissue, suggest that Cs-CaP composites loaded with MOX are valuable candidates for clinical trials aimed at osteomyelitis prevention [130].

Likewise, BCP, composed of HA and β-TCP, have gained significant attention for their dual potential in both eradicating infection and promoting bone regeneration [131]. BCPs are bioactive ceramics that combine HA and β-TCP in varying ratios, offering a unique balance between stability and resorbability. HA is highly stable and serves as an excellent scaffold for osteoconduction, supporting new bone formation. In contrast, β-TCP is more soluble, promoting the gradual resorption of the material and its replacement with natural bone [115]. The biphasic nature of BCPs allows them to gradually dissolve in the body, releasing calcium and phosphate ions into the surrounding biological environment, thereby facilitating new bone formation.

BCPs have been utilized in various forms, including bone cements, coatings, granules, scaffolds, and injectable systems, particularly for the treatment of osteomyelitis in cases involving bone defects or cavitary lesions [62]. After the surgical debridement of infected

tissue, BCPs are often used to fill the void left by the removal of necrotic bone. This not only stabilizes the bone structure but also supports the healing process by serving as a scaffold for new bone growth.

However, the use of BCPs in treating osteomyelitis presents certain challenges. Ensuring uniform drug distribution within the BCP matrix, preventing biofilm formation, and achieving optimal resorption rates remain key areas of ongoing research. Moreover, the long-term outcomes of BCP use in osteomyelitis, particularly in complex or chronic cases, require further clinical studies to establish standardized protocols and enhance treatment efficacy. Future developments may focus on improving the antibacterial properties of BCPs through surface modifications, incorporating novel antimicrobial agents, or developing composite materials that combine BCPs with other bioactive substances to enhance both bone regeneration and infection control.

Overall, while CaPs offer numerous advantages in biomedical applications, several challenges still need to be addressed to fully realize their potential. These challenges include their limited mechanical strength, the absence of an organic phase such as collagen, the presence of impurities, and inconsistencies in grain size and particle morphology, which can affect their performance [115]. Additionally, traditional processing techniques for fabricating these CaPs often suffer from extended production times, low yields, and difficulties in controlling porosity, which can limit their practical application [67].

4. Outcomes of Various Commercial CaPs for the Treatment of Bone Infection

The clinical outcomes of using CaPs for the treatment of bone infections have generally been favorable, with many patients experiencing successful infection resolution and significant bone regeneration. CaPs have proven effective not only in promoting bone healing but also in serving as carriers for antibiotics to combat infections. The main aspects of commercial CaPs are as follows.

(i) Antibiotic delivery and infection control: A critical advantage of CaPs in treating bone infections is their ability to deliver antibiotics directly to the infection site. Commercial products like Cerament® G and V, which are loaded with gentamicin and VAN, respectively, have been developed to release high concentrations of these antibiotics locally. Studies have demonstrated that antibiotic-loaded CaPs can significantly reduce infection rates in bone while minimizing the risk of systemic side effects associated with traditional antibiotic therapy. This localized treatment is particularly valuable in cases of chronic osteomyelitis, where biofilms may protect bacteria from systemic antibiotics [132]. Alternatively, another in vitro study aimed to compare the antibiotic loading (Gentamycin and Vancomycin) and release capacities of different commercially available bone graft substitutes, specifically Cerasorb® M (a synthetic, bioresorbable β-tricalcium phosphate material), Cerasorb® Flexible Foam (a flexible, resorbable, and porous scaffold made of β-TCP that adapts to irregular bone defects), and Osbone® (a highly porous, bioactive bone graft substitute composed of hydroxyapatite). The study evaluated the combination of antibiotics with different biomaterials, including β-TCP, HA, and β-TCP–collagen composites, to understand the influence of material structure (inner surface and porosity) on antibiotic loading and release. The results showed that all biomaterials tested exhibited adequate antibiotic loading capacity, with the antibiotics reaching the minimum inhibitory concentration within 24 h due to an initial burst release, followed by a slower, sustained release. The granulated materials (β-TCP and HA) demonstrated faster drug release compared to the β-TCP–collagen composite. However, the β-TCP–collagen composite showed a significantly stronger and longer release of gentamicin and vancomycin, suggesting a more sustained antibacterial effect, which may be beneficial for clinical treatment of bone infections. The study also confirmed that the antibiotics maintained their antibacterial activity against *S. aureus* and *Bacillus subtilis* after release from the biomaterials. Additionally, the osteoconductivity of the β-TCP–collagen composite may offer further benefits in bone infection treatment, supporting both antibacterial therapy and bone regeneration [133].

However, despite the benefits, achieving a controlled and sustained release profile of antibiotics from CaPs remains challenging. Inconsistent antibiotic release can lead to suboptimal therapeutic outcomes, potentially allowing bacterial resistance to develop or failing to maintain effective drug concentrations.

(ii) Bone regeneration: In addition to controlling infection, CaPs facilitate bone healing by providing a scaffold for new bone growth. For instance, a study reported that patients treated with Cerament® G not only had a reduced rate of reinfection but also exhibited significant bone regeneration [134]. In some cases, this led to successful limb salvage where amputation might have otherwise been necessary.

(iii) Challenges in CaP use: While the use of CaPs shows promise, several challenges remain. One key issue is the need for tailored degradation rates. CaP must degrade at a pace that matches the formation of new bone, ensuring that the material supports the bone until it is fully regenerated. If the CaP degrades too quickly, it may compromise structural integrity; if too slowly, it may interfere with natural bone remodeling. Additionally, optimizing the mechanical properties of the CaP to match those of the surrounding bone tissue is crucial to ensure the material can withstand the physical stresses of the body without causing implant failure.

Comparative studies have shown differences in the resorption rates and integration capabilities of various CaPs. For example, CS-based ceramics, like those in Cerament®, demonstrate more rapid resorption and integration with native bone compared to traditional HA-based materials, which tend to remain in the body longer but integrate more slowly [135]. The choice of CaP material should thus be tailored to the specific clinical scenario, considering factors like the size of the bone defect and the severity of the infection.

(iv) Long-term outcomes and complications: Although short- to medium-term outcomes of CaP use in bone infections is promising, long-term studies are essential to fully understand their efficacy and safety to avoid complications such as foreign body reactions and incomplete resorption, potentially leading to chronic inflammation or necessitating additional surgeries. Despite these concerns, CaPs have shown a high success rate in infection eradication and bone healing, particularly when integrated into a comprehensive treatment strategy that includes surgical debridement and systemic antibiotics.

(v) Biocompatibility and immune response: Long-term biocompatibility is another critical area of ongoing research. While many CaPs are generally well-tolerated, the potential for adverse immune responses remains, particularly with newer materials or formulations. Understanding the interactions between CaP and the immune system is crucial to ensuring their safety and effectiveness in long-term applications, especially given the diverse age groups and varying health conditions of patients. This knowledge will help tailor CaP treatments to individual patient needs, minimizing risks and maximizing therapeutic benefits.

In summary, the clinical outcomes of using CaPs to treat bone infections are highly dependent on various factors, including the specific material used, the type of microorganism causing the infection, the form of osteomyelitis, and the patient's overall health and age. While the results are generally positive, with many patients achieving infection resolution and bone regeneration, challenges remain. These include the need for tailored degradation rates, optimized mechanical properties, and consistent antibiotic release profiles over time. Moreover, ensuring long-term biocompatibility and understanding potential immune responses to certain materials are critical areas for future research. As advancements continue, the development of more sophisticated CaPs with enhanced properties is expected to further improve clinical outcomes and patient care in the treatment of bone infections.

5. Conclusions and Future Prospects

CaPs, especially HA and TCP, have emerged as potent solutions to the dual challenges of infection control and bone regeneration, with promising applications in the management of osteomyelitis. The inherent biocompatibility and osteoconductivity of CaP make them particularly valuable in bone tissue engineering, as they not only support new bone growth

but can also be tailored for localized drug delivery. By enabling the controlled, site-specific release of antibiotics, CaPs reduce systemic side effects typically associated with long-term antibiotic therapy and enhance the efficacy of osteomyelitis treatments. In practical terms, such targeted therapy holds potential to shorten treatment times, reduce the risk of recurrence, and lessen the burden on patients by minimizing the need for systemic antibiotics. Clinically, this could improve patient outcomes significantly, particularly for those suffering from chronic infections or requiring prolonged antibiotic regimens.

Looking forward, the optimization of CaP materials is likely to focus on refining structural and compositional properties at the micro- and nanoscales. Such advancements can enhance both mechanical durability and bioactivity, broadening the scope of CaP to address load-bearing needs in orthopedic and dental settings. Additionally, the development of CaP composites that incorporate antimicrobial agents—such as silver ions, peptides, and other bioactive molecules—has further strengthened their therapeutic value, providing a multifaceted approach to managing infection while supporting bone regeneration. This combined approach could enable personalized, infection-specific therapies, allowing clinicians to tailor treatments to individual patient needs, thereby advancing precision medicine within orthopedic and maxillofacial practices.

However, to translate these materials into widespread clinical use, there are challenges to overcome in ensuring their robust performance under real-world conditions. Enhancing the mechanical properties of CaP, such as their fracture toughness and load-bearing capabilities, is crucial for their application in high-stress areas of the skeleton. Furthermore, the development of sophisticated drug delivery systems that can finely control release kinetics will be essential to customize treatments for different clinical requirements, such as acute versus chronic infection management. These developments will be instrumental in widening the practical applications of CaP, potentially enabling their use across diverse patient populations and orthopedic needs, from spinal fusion procedures to complex reconstructive surgeries.

To achieve clinical adoption, additional in vivo studies and rigorous clinical trials are essential to validate the long-term safety, biocompatibility, and efficacy of CaPs across various orthopedic and dental applications. These studies will help establish standardized protocols and ensure patient safety, which are key to integrating CaPs as routine treatment options in healthcare settings. Furthermore, research into nanostructured CaPs, which allow greater control over cellular interactions and enhances regenerative outcomes, presents exciting opportunities for the future of personalized medicine and tissue engineering.

In conclusion, CaPs hold transformative potential in treating challenging bone conditions such as osteomyelitis. As advancements in material design and clinical integration continue, these materials are poised to play an increasingly central role in enhancing patient care by providing targeted, effective, and less invasive treatment options. The ongoing evolution of CaPs will likely expand their utility in clinical applications, ultimately contributing to improved patient outcomes and a broader range of therapeutic solutions in both orthopedic and dental medicine.

Author Contributions: Conceptualization, I.N. and C.S.F.O.; methodology, B.B.; software, B.B.; validation, I.N. and C.S.F.O.; formal analysis, I.N. and C.S.F.O.; resources, I.N. and C.S.F.O.; data curation, B.B.; writing—original draft preparation, I.N. and C.S.F.O.; writing—review and editing, I.N., C.S.F.O. and B.B.; visualization, C.S.F.O.; supervision, I.N.; project administration, C.S.F.O. and I.N.; funding acquisition, C.S.F.O. and I.N. All authors have read and agreed to the published version of the manuscript.

Funding: I.N. and B.B. acknowledge the support from a grant of the Ministry of Research, Innovation and Digitalization, CNCS -UEFISCDI, project number PN-IV-P8-8.3-ROMD-2023-0060, within PNCDI IV. This research was supported by the Romanian Ministry of Research, Innovation and Digitalization under the Romanian National Nucleu Program LAPLAS VII—contract no. 30N/2023. C.S.O acknowledges the financial support from the integrated project be@t—textile Bioeconomy (TC-C12-i01, Sustainable Bioeconomy No. 02/C12—i01.01/20229, promoted by the Recovery and Resilience plan (PRR), Next Generation EU, for the 2021–2026 period. C.S.F.O was also supported by FCT—Fundação

para a Ciência e a Tecnologia, through the Project UIDB/50016/2020. B.B. acknowledges the Core Program with the National Research Development and Innovation Plan 2022–2027, carried out with the support of MCID, project no. PN 23 05 and by the Ministry of Research and Innovation through Program I—Development of the National R&D System, Subprogram 1.2—Institutional Performance—Projects for Excellence Financing in RDI, contract no. 18PFE/30.12.2021.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

List of Abbreviations

α-TCP	alpha-tricalcium phosphate
β-TCP	beta-tricalcium phosphate
μCT	micro-computed tomography
AC	apatite cement
Ag-THA	silver and tanin-modified hydroxyapatite
AgNPs	silver nanoparticles
BAFo	bone area fraction occupancy
BCP	biphasic calcium phosphate
BMP-2	bone morphogenetic protein-2
BMSCs	bone marrow mesenchymal stem cells
CaP	calcium phosphate
CaPC	calcium phosphate cement
CS	calcium sulfate
Cs	chitosan
DAA	dual acid-etched
DCPD	dicalcium phosphate di-hydrate
FGF	fibroblast growth factor
HA	hydroxyapatite
HA-TiO_2	hydroxyapatite–titania
IV	intravenous
LDH	lactate dehydrogenase
MgHA	magnesium-doped hydroxyapatite
MOX	moxifloxacin hydrochloride
MRSA	methicilin-resistant *Staphylococcus aureus*
MWCNTs	multi-walled carbon nanotubes
PBA	pulverized autograft
PEC	polyelectrolyte complex
PLGA	poly(lactic co-glycolic) acid
PMMA	polymethylmethacrylate
SEM	scanning electron microscopy
Sim-HA	simvastatin and hydroxyapatite
TCP	tricalcium phosphate
TNT	titanium nanotube
VAN	vancomycin
ZFHA	zinc- and iron-doped hydroxyapatite
Zn-HA	zinc-doped hydroxyapatite

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