# Adjunctive Therapies in the Treatment of Osteomyelitis

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**ABSTRACT**

The current management for chronic osteomyelitis centers on adequate antibiotic coverage and surgical debridement of nonviable tissue. The eradication of osteomyelitis, however, often involves a prolonged and frustrating course of management. Nonsurgical adjunctive modalities have not been widely used, mostly due to a lack of perceived efficacy, and have remained in a state of infancy. In this article, we will outline the rationale, current status, and evidence for several potential adjuncts to osteomyelitis management.

**KEYWORDS:** Osteomyelitis, adjunctive therapy, hyperbaric oxygen therapy, biofilm, growth factor

Although bone is typically resistant to infection, osteomyelitis can nevertheless arise from a variety of disease processes and trauma. Eradication of osteomyelitis often involves a prolonged, frustrating course of management, as the infectious process is typically refractory to conservative measures or a short course of antibiotics. It arises most commonly secondary to a contiguous focus of infection such as an open fracture or an infected prosthesis. In the context of plastic surgical practice, osteomyelitis is most often seen in irradiated wounds, contaminated fractures, pressure sores, and diabetic foot wounds. In terms of outcomes, osteomyelitis has a significant impact on quality of life for the patient and on financial burdens for the health care system.

The current management for osteomyelitis centers on adequate antibiotic coverage and surgical debridement of nonviable tissue.[1,2] Whereas acute hematogenous osteomyelitis might respond favorably to a course of antibiotics alone, more complex presentations may require extensive surgical debridement in addition to an aggressive antibiotic regimen for successful treatment. Such surgical interventions often leave substantial defects, which in turn will require major reconstructive efforts such as tissue flaps and vascularized bone grafts. Even with standard care, therapeutic failures and recurrences are common, often in the range 20 to 30%.[3,4] For patients such as the diabetic population, the consequences of treatment failure may escalate to limb loss. Indeed, one of the most common reasons leading to a toe or foot amputation in a diabetic patient is the presence of underlying osteomyelitis with associated soft tissue sepsis.[5]

Significant strides have been made in the antibiotic regimens and surgical options available to clinicians managing osteomyelitis. Various parenteral antibiotic alternatives exist in the armamentarium against the pathogenic microorganisms. Surgical interventions have advanced with use of vascularized bone grafts, free flaps, and antibiotic beads to complement the necessary debridement; these approaches are discussed elsewhere in this issue.[2]

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As the local vascularity to bone is essentially impaired in the setting of osteomyelitis, regardless of the pathogenesis, strategies to improve blood supply and tissue perfusion will serve to minimize recurrence in predisposed wounds and improve microbial clearance in affected areas. The approaches to accomplish this goal have typically been surgical, with recruitment of tissue flaps and adequate debridement. Nonsurgical adjunctive modalities have not been widely used, mostly due to a lack of perceived efficacy, and have remained in a state of infancy. Most of these adjunctive therapies have yet to be rigorously tested in randomized, prospective clinical trials, and thus, they carry with them the attendant negative implications for clinical acceptance as well as payer reimbursement.

In this article, we will outline the rationale, current status, and evidence for several potential adjuncts to osteomyelitis management. Hyperbaric oxygen therapy (HBOT) has perhaps the longest history of reported efficacy in treating refractory cases of osteomyelitis.[2,6–9] Acceptance of its use has grown, although controversy still remains because no high-quality clinical studies exist. Growth factors such as the bone morphogenetic proteins (BMPs) have been studied extensively for their effects in modulating osteogenesis. Their potential as therapeutic adjuncts in osteomyelitis is apparent in the few studies that have been performed in animal models, but further studies are necessary to determine their ultimate clinical utility.[10–13] Bacterial biofilms are known to develop over the surface of devices such as those used for internal fixation of a fracture and are involved in the pathogenesis of osteomyelitis.[14] With the rapid advancements in biofilm research, the possibility of exploiting biofilm microbiology to bolster current therapies is promising. Other hypothetical adjuncts such as platelet-rich plasma (PRP), pulsed electromagnetic fields (PEMFs), and ultrasound are still speculative and have not been extensively investigated in the setting of infection at this time.

## GENERAL PRINICPLES OF OSTEOMYELITIS TREATMENT

Osteomyelitis is generally considered to be chronic if the clinical signs have persisted for greater than several months or if the infection has recurred or relapsed. Nevertheless, the presentation of this condition can progress much more insidiously over many months or years. The common etiologies are broadly divided into the following categories: contiguous infection, diabetes or vascular insufficiency, and hematogenous source.[1] Pathogenic microorganisms are most often *Staphylococcus aureus* but can also include *Streptococcus*, *Pseudomonas*, or enteric gram-negative bacteria.[1,15]

Once diagnosed, the identification of the causative microorganisms is ideally obtained with specimens from a surgical or needle biopsy to provide the best guidance for antibiotic therapy. Typical regimens involve at least 4 to 6 weeks of parenteral administration, although conversion to oral antibiotics is possible in appropriate cases with agents such as clindamycin or fluoroquinolones. Other treatment alternatives that have gained increased acceptance include outpatient parenteral therapy and combination regimens with agents such as rifampin. More recently, newer antibiotics such as linezolid have shown promise for the treatment of resistant microorganisms in osteomyelitis.[16] Antimicrobial therapy is more thoroughly discussed in the article by Fraimow in this issue of the journal.

Although antibiotic therapy will always constitute a major component of osteomyelitis treatment, the challenges for successful treatment revolve around the interface of impaired vascularity that develops in the regions of infected bone. Sequestra (devitalized areas of infected bone), which form in chronic osteomyelitis, simply cannot be reached adequately by leukocytes or perfused in sufficient concentrations by systemic antibiotics. Even in the surrounding areas of living bone, the tissue is still compromised by the relative hypoperfusion resulting from the inflammatory process that impairs blood flow within the vascular channels.

The debridement of necrotic tissue and the restoration of viable vascularity to the infected site have been the goals of the surgical component to osteomyelitis treatment. Traditional surgical philosophy emphasizes the thorough excision of necrotic and infected tissue to the point of healthy bleeding (paprika sign). Unfortunately, the results of adequate tissue debridement can often leave a considerable defect.

In recent years, several advancements have improved the management of the resultant dead space. Multiple techniques of tissue transfer, including myocutaneous flaps and vascularized bone grafts, have increased the success rate in restoring the defect with viable tissue and vascularity. Antibiotic beads have increased the surgeon's ability to provide local antimicrobial control after debridement. Other methods have included the Ilizarov technique, which produces distraction osteogenesis that results in highly vascular new bone.

## ADJUNCTIVE THERAPIES FOR CHRONIC OSTEOMYELITIS

### Hyperbaric Oxygen Therapy

HBOT involves the intermittent inhalation of 100% oxygen in specialized chambers at pressures greater than that at sea level ($>1$ atm absolute; ATA). Typical protocols recommended by the Undersea and Hyperbaric Medical Society (UHMS) for treating wounds expose the patient to pressures of 2 to 2.5 ATA lasting

90 to 120 minutes per session for ~40 treatments. The arterial partial pressure of oxygen rises to ~1500 mm Hg under these hyperbaric conditions; oxygen tensions can approach 500 mm Hg in soft tissue and 200 mm Hg in bone.[8,9]

The hypothesis that raising oxygen tension within the soft tissue and bone can enhance the treatment of chronic osteomyelitis stems from lines of evidence similar to those that exist in the many other conditions for which HBOT has been applied. Osteomyelitic bone has been shown to be hypoxic with a partial pressure of 20 to 25 mm Hg in animal models, and this oxygen content can be dramatically raised in hyperbaric conditions.[17,18] In the presence of infection, the phagocytic and bactericidal ability of leukocytes parallels the oxygen tension in the tissue. Although the hypoxic conditions in the diseased bone reduce the ability of neutrophils to generate the reactive oxygen species necessary to kill bacteria, hyperbaric oxygen (HBO) can enhance this bactericidal activity.[17–20] The processes of collagen synthesis and osteogenesis are inhibited in a hypoxic state, and studies have suggested that improved oxygen tension can normalize if not enhance these functions.[17,18,21,22] Other efforts have provided evidence for the effects of HBO in inducing angiogenesis, suppressing anaerobic organisms, and enhancing antibiotic activity.[18,22–24]

HBOT is being increasingly used for several conditions, including chronic osteomyelitis. Clinical studies of HBOT vary in quality depending on the indication, but the overall body of evidence for bony healing is characterized by a paucity of well-controlled or randomized trials. A Cochrane review evaluating the literature from 1966 to 2003 for studies on use of HBOT in fracture healing and nonunion treatment, albeit not specifically osteomyelitis cases, identified 68 references but failed to find any randomized evidence to support or refute the indication of HBOT.[25] A recent review performed for the Center of Medicare and Medicaid Services to assess use of HBOT in treating different classes of hypoxic wounds had found 57 mostly nonrandomized studies published between 1998 and 2001.[26] In this review, Wang et al concluded that these studies as a group suggested HBOT had potential beneficial adjunctive effects for conditions such as chronic nonhealing diabetic wounds, compromised skin grafts, osteoradionecrosis, soft tissue radionecrosis, gas gangrene, and chronic osteomyelitis. One nonrandomized controlled trial and one case series specifically studying chronic osteomyelitis were identified, but these studies were found to be inconsistent in their reported results.[27,28] Nevertheless, it is notable that Medicare currently provides coverage for those patients receiving HBO as adjunctive therapy for chronic osteomyelitis that is not responding to standard medical and surgical treatment.[29]

Although high-quality clinical trials may not be available, several retrospective reports have been published in the recent literature. Despite the inherent weaknesses of these studies, they do suggest great potential for HBOT in the treatment of chronic osteomyelitis. In a recent small series, Lentrodt et al reported the successful treatment of a group of three juvenile patients with recurrent mandibular osteomyelitis.[30] These patients had elected to receive HBOT along with a standard high-dose antibiotic regimen. One of the three patients had multiple recurrences during HBOT and received an extended regimen, but the other two patients were treated with 40 sessions as suggested by the UHMS. After completion of HBOT, all three patients were reported to have been free of symptoms during the following period of 20 to 74 months. An important aspect of this study is the fact that these juveniles were spared conventional surgical interventions, which can result in comorbidities, including disfigurement. In another case series of 13 patients with chronic refractory osteomyelitis of the femur, Chen et al reported successful treatment for 12 of the patients after adding HBOT as an adjunct to surgery and antibiotics.[6,7] For the average follow-up period of 22 months after cessation of HBOT, the patients have apparently remained free of recurrent symptoms. Additionally, the patients were reported to have been unresponsive to the surgical and antibiotic regimen before the implementation of HBOT. At least one controlled but nonrandomized trial assessing the utility of HBOT in treating chronic osteomyelitis has been reported in the literature.[31] Twenty-eight patients were followed in this study, but the authors concluded that there were no significant effects on length of hospitalization, rapidity of wound repair, initial clinical outcome, or recurrence of infection.

Part of the challenge in studying HBOT efficacy in osteomyelitis is the fact that rigorous assessments of meaningful parameters are difficult to achieve. Radiographic findings are imprecise, magnetic resonance imaging (MRI) is expensive, serial cultures are impractical, and inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are also imprecise. Bearing these limitations in mind, the available clinical data still seem promising. Nevertheless, better trials are needed to further study the application of HBOT in chronic osteomyelitis, as clear guidelines and consensus remain lacking.

## Growth Factor Therapy/Gene Therapy

Growth factors such as the BMPs are known to play important roles in skeletal development and bone formation. Multiple studies have demonstrated the positive effects of exogenous BMPs in accelerating osteogenesis and bone healing in animal models. Growth factor

therapy and gene therapy have only recently received attention as potential therapeutic adjuncts to the management of chronic osteomyelitis, and their clinical utility remains speculative at this time.

Only a few animal studies have been reported in recent years evaluating the effects of either growth factor therapy or gene therapy in the setting of osteomyelitis. Chen et al first reported in 2002 that recombinant human osteogenic protein-1 (rhOP-1, or BMP-7) could induce bone formation in an acutely infected rat femur fracture model.[10] The rat model was designed as an internally stabilized femoral segmental defect, which was subsequently inoculated with *S. aureus* to establish an infection. This group's results suggested that rhOP-1 was effective in promoting osteogenesis in the setting of infection, although not to the same degree as in uninfected bone. More recently, Chen et al have reported that rhOP-1 could induce new bone formation in a chronically infected variant of the rat fracture model.[11] In this study, they also found that the osteogenic effects of rhOP-1 were enhanced when combined with systemic antibiotic administration. Results from these studies support the premise that growth factors may have therapeutic potential in an infected field. Further investigation is warranted to continue exploring the biology and clinical applicability of growth factors in chronic osteomyelitis management.

A recent study by Southwood et al evaluated the utility of a gene therapy approach with adenoviral vectors to deliver a BMP-2 gene (Ad-BMP-2) to enhance bone healing in the setting of osteomyelitis.[32] Using a rabbit femur fracture model, the investigators inoculated the bony defects percutaneously with *S. aureus* to establish an infection. Gene transfer was accomplished by directly injecting the Ad-BMP-2 vectors into the fracture defect. The mixed results from this study revealed a temporary trend of earlier initial and bridging callus formation in the Ad-BMP-2–treated fractures, although no differences between treatment groups were seen at 16 weeks. Such findings suggest that gene therapy may have hope of becoming a possible solution to the difficult problem of growth factor delivery in infected conditions. Advantages of effective gene transfer could include increased consistency of growth factor release into the wound bed, increased growth factor production by the resident cells, and ability to deliver treatments locally, among others. On the other hand, the similarities of the hostile environment in an osteomyelitis infection to that of a chronic cutaneous wound may remain difficult obstacles to overcome for growth factor–based therapies. This detrimental milieu of growth factor–degrading proteases, low pH, and excessive bystander cellular damage has continued to be one of the frustrating challenges to developing wound-healing therapeutics.

## Biofilm Microbiology

A significant advancement in our understanding of chronic infections has been the elucidation of the genetic and molecular biology of bacterial biofilms. These sessile communities of bacteria reside on surfaces and are enveloped by protective polymeric matrices that are notoriously resistant to both host immune responses and conventional antibiotics. Biofilms have been linked to the pathogenesis of various human chronic infections, including dental caries, endocarditis, cystic fibrosis pneumonia, and osteomyelitis.[14,33]

Bacteria form biofilms on surfaces such those of catheters and prostheses, in addition to devitalized tissue such as the sequestra found in chronic osteomyelitis. It is thought that the establishment of these structures is a natural part of the life cycle of bacteria when they are in starvation mode, facing unfavorable environments, or colonizing a wound. Biofilms are not formed independently by individual bacteria; rather, they arise from a cooperative organization of bacterial cells with different members playing separate roles and communicating to each other. The resulting complex structure is capable of functions that promote survival of the resident bacteria, such as attachment to a surface in adverse environments, supply of nutrients to its members through the connecting channels in its matrix, inhibition of antibiotic penetration, and dissemination of planktonic members.[14,33]

The formation of biofilms has been proposed as a major pathogenic factor in the development of chronic osteomyelitis, whether or not the infection is associated with prosthetic devices.[14,34] In a recent review, Costerton correlates the clinical observations in osteomyelitis to the microbiology of biofilms and the evidence of biofilm involvement.[14] Pathologic features such as the resistance of osteomyelitis to systemic antibiotics, the chronicity of osteomyelitis, the constant source of inflammatory stimuli, and the frequent necessity of sharp debridement or removal of a device to eradicate the infection can be attributed to the effects of a biofilm presence.

Multiple animal studies have evaluated the role of biofilms in the pathogenesis of osteomyelitis.[34–36] Some of the seminal studies were performed in a rabbit model of osteomyelitis.[34,35] Osteomyelitis was induced in this model by the introduction of bacterial cells along with the implantation of a silicone catheter into the tibial medullary cavity. Examination of the infected bone by electron microscopy revealed that the bacteria cells were present in a biofilm along the surfaces of both the catheter and the bone. Similarly, other studies have used electron microscopy to analyze osteomyelitic bone specimens from human subjects and have provided some of the first direct evidence that bacteria cells in this setting also adhered to devitalized bone in a biofilm.[34]

Recent progress in the understanding of biofilm microbiology has opened the doors to exciting new approaches that may soon become realistic and valuable

components to the current treatment paradigm of osteomyelitis. Perhaps most intriguing has been the elucidation of the cell-to-cell signaling that occurs among the community of bacteria as a biofilm develops and matures. This mode of communication is essential for the bacterial cells to organize themselves into a biofilm. Some of the identified signaling molecules have a "quorum-sensing" functionality that activates specific gene pathways in the appropriate conditions, which lead to the development of a biofilm.[14] Prevention of biofilm formation by inhibiting these quorum-sensing signals or by the manipulation of other similar pathways is currently an area of intensive research. The ribonucleic acid III inhibiting peptide (RIP) is one example of these signals that has been shown in multiple animal studies to prevent the formation of *Staphylococcus* biofilms.[37–39] RIP disrupts the activity of the target of ribonucleic acid III activating protein (TRAP) and leads to a downregulation of the gene expression necessary for biofilms to form. Its effects in osteomyelitis have been evaluated in at least one animal model. Using a rabbit tibial osteomyelitis model, Balaban et al reported that RIP could significantly reduce the ability of *Staphylococcus* bacteria to establish an infection and destroy bone.[39] Additional studies will undoubtedly continue to uncover the biology of biofilms in osteomyelitis, and it appears hopeful that this direction of research will translate into clinically useful therapeutics.

## Pulsed Electromagnetic Fields/Ultrasound

The application of PEMF stimulation was first approved by the U.S. Food and Drug Administration (FDA) in 1979 for treating fracture nonunions and has received increasing attention for various other indications since that time. The clinical utility of these devices in fracture healing rests on the hypothesis that the cellular processes of bone formation are regulated by the generation of electrical potentials. PEMFs are believed to simulate the endogenous electrical fields that are produced by bone in response to mechanical strain. This response of bone to physical loads is believed to stimulate new bone growth. The mechanisms of action for PEMF on a molecular level are thought to involve the upregulation of cytokines such as TGF-β, BMP-2, bFGF, and BMP-7. Numerous experimental animal models and clinical trials have evaluated the effects of PEMF stimulation on fracture healing and have demonstrated improved bone formation and accelerated union.[40–42]

Low-intensity ultrasound is another physical energy modality that has been approved by the FDA for use in treating fractures. Approval was granted for treating fresh fractures in 1994 and established nonunions in 2000.[40] Mechanisms by which ultrasound energy accelerates bone repair seem to affect each of the main stages of the healing process: inflammation, repair, and remodeling.[40,43] In particular, studies have provided evidence of the effects of ultrasound in upregulating inflammatory gene expression,[44,45] promoting angiogenesis and increasing vascularity,[46] and stimulating proteoglycan synthesis.[44,45]

As an adjunct for accelerating bone healing, use of physical energy has been evaluated in various studies and has received FDA approval as in the above examples. Hypothetically, the molecular pathways that are activated by these modalities to improve healing may also potentially play a beneficial role in bolstering the host response against an infection. Specifically, their effects on local perfusion and angiogenesis may prove to be the most significant in the setting of osteomyelitis. It has also been suggested that electrical fields or ultrasound can be efficacious in disrupting the attachment of biofilms.[47] Studies performed with in vitro biofilm models have suggested that the delivery of this type of energy not only directly interferes with biofilm formation but can also act synergistically with antibiotics to enhance their activity.[48]

## Platelet-Rich Plasma

PRP is the isolated concentrate of autologous blood containing the plasma fraction with a platelet concentration above baseline levels. It can be produced by using a variety of methods, such as standard laboratory centrifuges, cell separator and salvage devices, and specialized, compact office systems. Multiple clinical applications have been reported for use of PRP to improve healing, primarily in periodontal and oral surgery, maxillofacial surgery, aesthetic surgery, spinal fusion, heart bypass surgery, and chronic wounds.[49]

Platelets are known to play a significant role in wound healing by secreting many vulnerary factors into the wound milieu. These proteins include growth factors, cytokines, and chemokines, and they regulate the progression of wound healing though the inflammatory, proliferative, and remodeling stages. Studies have shown that increasing the concentration of platelets and their resultant secretory proteins can enhance the proliferation of cells such as fibroblasts and mesenchymal stem cells in the wound.[50] Along this line of inquiry, animal models and clinical trials have also suggested that PRP can enhance both hard and soft tissue healing.[49,51]

The utility of PRP in the setting of osteomyelitis currently remains unknown. Given the vulnerary effects that are apparent in soft tissue healing and also bone healing, one may speculate that these effects may also enhance healing in a wound or fracture complicated by osteomyelitis. As with the other adjunctive modalities, it could be likely that the value of PRP for the osteomyelitic lesion may lie in its potential ability to enhance angiogenesis and local perfusion to the region.

## CONCLUSION

The development of future modalities for the treatment of osteomyelitis remains an immature field. The current adjunctive therapies seem promising but require more investigation into their clinical efficacies. Also, the possible utility of combination therapies deserves to be explored. The most successful approaches for this difficult clinical problem may be those that address the compromised vascularity surrounding osteomyelitic foci. Additionally, we believe that the recent advancements in the understanding of biofilm microbiology should vault this aspect of osteomyelitis pathogenesis into the forefront of efforts to develop new therapies.

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