OTA Meeting Symposium

Orthopaedic infections: novel treatment strategies and evolving concepts

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Abstract Orthopaedic infections remain challenging complications to treat, with profound economic impact in addition to patient morbidity. The overall rate of infection following orthopaedic surgery with internal fixation devices has been estimated at 5%, with hospital costs 8 times that of those without fracture-related infections and with significantly poorer outcomes regarding function and pain. Fracture-related infections (FRIs) occur in approximately 20% of all trauma cases, and treatment has evolved very little over the years. While union can be achieved 70%–89% of the time, long-term recurrence rates vary between 9% and 58% and retention of implants is only around 30%–40%. This is underscored by the financial, psychosocial, and physical burden placed on the patients. The difficult management of FRIs is multifactorial; however, a major contributor is biofilm. Alternative treatment strategies to combat biofilm have come in the form of photodynamic therapy and bacteriophage therapy. Use of local antibiotic therapy in the form of powder and dissolvable antibiotic beads has continued to be expanded, with new applications explored. Systemic antibiotic use has continued to be optimized, with new treatment protocols calling for per os (PO) administration as opposed to intravenous. In conclusion, orthopaedic infections remain difficult clinical dilemmas, although evolving prevention and treatment modalities continue to emerge.

Keywords: infection, bacteriophage, photodynamic therapy

1. Applying Antimicrobial Photodynamic Therapy to Orthopaedic Wounds

Biofilms, characterized as complex aggregates of microorganisms encapsulated within a three-dimensional gelatinous matrix, present formidable challenges in medical treatment across various contexts. Defined by their intricate structural and functional heterogeneity, biofilms mimic the organizational complexity of multicellular organisms. Biofilms should be thought of as a complex organism able to react to its environment rather than an inert shelter for bacteria and are made up of numerous microcolonies of bacteria tightly packed together and surrounded by a hydrogel layer that provides a barrier to the surrounding environment. These microbial communities exhibit diverse capabilities, such as enhanced nutrient scavenging and varying growth rates dependent on their position within the spatial structure, which confer significant survival advantages. In addition, biofilms demonstrate increased virulence and stabilized protection, complicating efforts to treat associated infections effectively. They offer multiple different layers of protection against antibiotic therapy, including resistance at the surface, resistance within the microenvironment, and resistance at a cellular level.

Significant insights have been gained from adjacent medical fields such as cystic fibrosis, otitis media, and urinary tract infections, where studies have documented the synergistic behaviors of microbial communities within biofilms. These behaviors significantly affect treatment outcomes and the progression of infection. In orthopaedic settings, understanding the ecological dynamics of biofilm communities could lead to more effective treatment strategies that consider the microbial interactions within these complex structures.

There are several illustrative examples of these complex interactions in other medical specialties that may inform future research within orthopaedic trauma. Wucher et al[1] demonstrated that during coinfection with *V. cholera* and *E. coli*, *E. coli* that is embedded within *V. cholera* cell groups can evade phage attacks, resulting in enhanced survival. Similarly, in models of cystic fibrosis lung infection, coinfection of *Pseudomonas* and *Staphylococcus aureus* has demonstrated enhanced survival of *Staphylococcus* in the presence of vancomycin.[2] In another study,

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Pseudomonas appeared to sense the presence of *Staphylococcus* and move toward it in an effort to form a mutually beneficial mixed colony.[3] However, antagonistic or competitive relationships can have important treatment-related effects as well. Oliviera et al[4] demonstrated that when there is interspecies competition, more biofilms are formed. There is also evidence that other stressors such as exposure to antibiotics increase biofilm formation.[5] These examples highlight the potential for biofilms in orthopaedic infections to facilitate mutually beneficial or even competitive relationships among different microbial species, which can alter the effectiveness of conventional treatments.

Despite these complexities, current treatment modalities often fall short, particularly because they do not specifically target the unique properties of biofilms. This realization has spurred interest in developing new therapeutic strategies that can more effectively disrupt these microbial communities. One promising approach is photodynamic therapy (PDT), which involves the application of a photosensitizing agent—such as 5-aminolevulinic acid (5-ALA), a compound with a long track record of safety and efficacy—that is preferentially taken up by microbial cells. On exposure to a specific wavelength of light, 5-ALA is activated, producing cytotoxic singlet oxygen and free radicals that kill the biofilm organisms. This method benefits from the conserved nature of the porphyrin pathway across bacterial species, ensuring broad-spectrum activity that is unaffected by traditional antibiotic resistance mechanisms.

Preliminary research using sophisticated high-fidelity microfluidic models of biofilm has demonstrated that PDT can eradicate up to 98% of biofilm, significantly outperforming other common treatment methods including topical antibiotics (vancomycin/tobramycin), chlorhexidine, Bactisure, Dakin's, and Betadine (Fig. 1). These promising results have led to further investigations around applying PDT to manage several clinical conditions: (1) prevent infection in contaminated high-risk open fracture; (2) eradicate ongoing contamination/biofilm at the implant–skin interface in osseointegrated prostheses; and (3) treat fracture-related infection. We are currently conducting NIH-funded studies using an animal model of a blast-impact type IIIA open tibia fracture to explore the dose and efficacy in this population. We know that bacterial communities and biofilms begin to develop within hours. We believe that intervening early to prevent initial contamination and initial development of biofilm in an open fracture has the potential to have a real impact on infection prevention. We are also working on applying PDT to an animal model of osseointegrated prosthesis and are in early stages of translation into an early-phase human trial, funded by the Department of Defense and the NIH. Regarding fracture-related infection, we anticipate that a higher PDT dose will be needed and that the PDT will be most effectively delivered either in the operating room or through a surgical implanted catheter for repeat PDT sessions postoperatively. We anticipate that this emerging research may transform the prevention and treatment of fracture-related infections. We firmly believe that a new approach to thinking about and studying biofilm communities as well is essential to advance clinical practice.

2. Bacteriophages: What Are They and How Can They Help?

2.1. What Are Bacteriophages?

Bacteriophages (phages) can be simplistically thought of as viruses for bacteria.

A very basic summarization of their mechanism is as follows: attachment to the cell, injection of genetic material, replication of bacteriophages, lysis of the cell, and release of phages. These released phages then go on to "infect" other bacterial cells until either the infection is eradicated or a steady state of bacterial replication and bacteriophage infection occurs.

Bacteriophages offer several advantages: they do not affect eukaryotic cells, are bactericidal, show minimal disruption of normal flora, narrow potential for resistance, do not have cross-resistance with antibiotics, and have biofilm clearance capabilities. However, to really understand why current strategies struggle and how phages can help us, we need an understanding of biofilms.

2.2. Resistance at the Surface

- Antibiotics *can* penetrate biofilm; it is just that they are not effective once they do. The first line of defense occurs at the surface of the biofilm. The outer layer of biofilm slows the rate of penetration of antibiotics, meaning that concentrations will never reach a necessary level to be therapeutic.

2.3. Resistance Within the Microenvironment

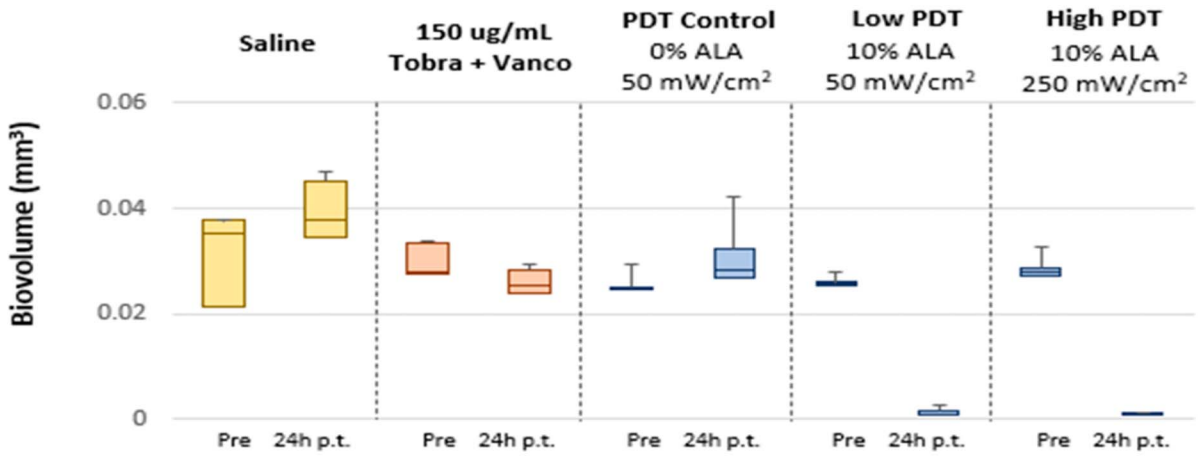
- Once antibiotics penetrate the surface layer, they encounter the layered microcolonies of bacteria. The hydrogel layer and tight packing of microcolonies offer other lines of defense. This further slows/limits the penetration of antibiotics and decreases their ability to reach appropriate concentrations.
- As the antibiotics move deeper into the biofilm, they encounter an increasingly hostile environment, which becomes more anaerobic and acidic. This directly antagonizes the activity of drugs such as tobramycin, ciprofloxacin, and aminoglycosides, with deeper levels of the biofilm being so acidic that most antibiotics are rendered ineffective.

2.4. Resistance at a Cellular Level

- As the antibiotics penetrate and begin to encounter microcolonies, some gain access to the bacteria within. However, because they cannot do so at high enough concentrations, this allows bacteria to adapt. Once a bacterial cell upregulates its efflux pumps, produces beta-lactamases, etc. in response to the antibiotic, it begins communicating through quorum sensing, allowing for rapid adaptation of all the bacteria within the microcolony.
- The resistant microcolony then communicates through channels to other microcolonies telling them to adapt. A microcolony can thus develop resistance to an antibiotic before the antibiotic has even encountered the colony.
- As antibiotics move deeper into the biofilm, they encounter highly resistant phenotypes of bacteria and bacterial forms called "persister cells." Persisters are dormant bacteria that have entered a spore-like state capable of withstanding extreme environments. These "spores" are not in a different genetic makeup than the rest of the bacteria present in the biofilm, just in a different state. This state is completely resistant to antibiotics, meaning that if an antibiotic were present and able to eradicate all the microcolonies present within the biofilm, as soon as the antibiotics were removed, the persister would become active again, changing back into their sessile or planktonic forms.

A

Treatment	Saline	150 ug/mL Tobra+Vanco	PDT Control 0% ALA 50 mW/cm2	Low PDT 10% ALA 50 mW/cm2	High PDT 10% ALA 250 mW/cm2
Effect	+25%	-30.7%	+22.9%	-94.5%	-96.4%
Significance	NS	<0.05	NS	<0.001	<0.001



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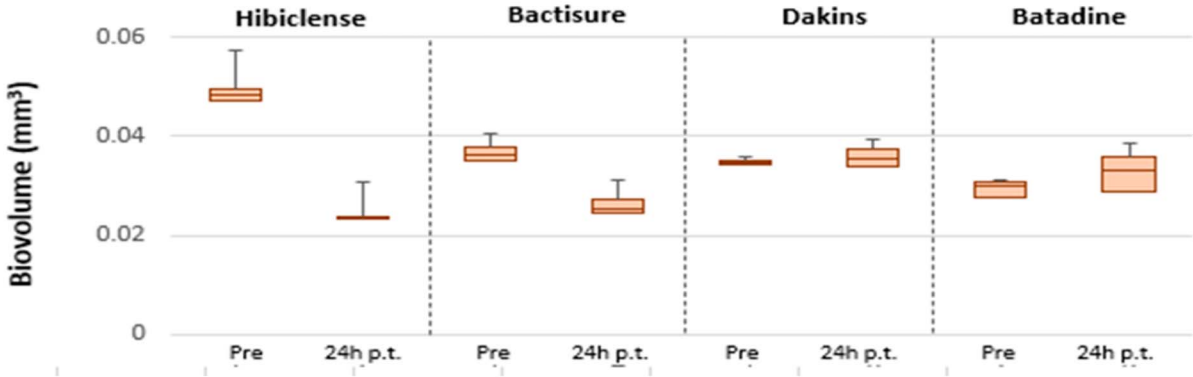

Figure 1. (A) The use of low and high photodynamic therapy shows significantly decreased biovolume in comparison with saline and vancomycin/tobramycin. (B) The effects of chlorhexidine, Bactisure, Dakin's, and Betadine on biovolume compared with photodynamic therapy.

2.5. Phages Versus Biofilm

Phages also have difficulty penetrating the thick structure of biofilm, and there are several factors that can contribute to biofilm phage resistance; however, phages have mechanisms for this. Phages produce a variety of enzymes whose sole function is to breakdown extracellular polymeric substances (EPS). Depolymerases, lysins, proteases, etc are all secreted by bacteriophages to breakdown EPS, dissolving biofilm. These enzymes, among others, allow for deep penetration of phages into the biofilm and direct access to bacterial cells, thus circumventing some of the antibiotic challenges of resistance at the surface.

Once they have access to the bacteria, they attach to the cell surface. This step has no link to antibiotic resistance. If the bacteria are susceptible to the phage, infection will occur. Theoretically, 1 phage infecting 1 bacterium is all that is necessary to begin the eradication of the infection, meaning that the effectiveness is not dependent on reaching some level of therapeutic concentrations (although there is available research on optimal concentrations for therapy).

Persister cells are problematic, even for bacteriophages; however, they are not immune. While a persister cell may be metabolically inactive, they still contain receptor-binding proteins on the surface that phages can interact with. While we know that phages can infect and eradicate persister cells, the mechanism is not clearly defined.

While the resistance mechanisms for antibiotics can still present a challenge for phages (plus additional phage resistance mechanisms), none of them are completely effective and phages have developed to be a much more effective solution to bacteria and biofilm when compared with antibiotics.

2.6. Summary

Phages offer a promising alternative to infection control, especially considering the concern with multidrug-resistant

infections. They are effective against biofilm and multidrug resistant bacteria; however, more data are needed.

3. Infection Prevention in Open Fractures—How to Go From (Very) Good to Great

Open fractures have some of the highest infection rates of any injury, and it is for good reason. Exposed bone, gross contamination, injured or missing soft-tissue envelope, and a patient with comorbidities or polytrauma are some of the primary reasons for infection. In addition, some of the treatments required for fracture stabilization and union can increase the likelihood of infection as both bone grafts and internal fixation are foreign bodies that provide a surface for bacteria to grow. The infection rates seem to be about the same for the past several decades, and a recent prospective study on severe open fractures in civilians[6] along with a retrospective study from the military both reported a 27% deep infection rate.[7] With the assumption that there will not be a single new product or practice that will appreciably reduce infection rates, the best approach is to bring better practice or products for each touchpoint of the patient along the continuum of care.

3.1. Early Anti-Infection

Bacteria replicate quickly and can form a biofilm that makes them recalcitrant to most antibiotics and immune response, so it makes sense to kill the bacteria before they can become established. Recently, there is an increased awareness of the need to administer antibiotics as soon as possible after injury; 1 recent study suggests that if antibiotics are given in the first hour, there is a decreased rate.[8] Despite this, there are still infections, and it could be because of lack of gram-negative coverage or poor antibiotic penetration in patients with the most contaminated and compromised soft-tissue envelopes. A new therapy that allows empiric use and provides gram-negative coverage and does not increase resistance would be beneficial. Worth noting, cefazolin does, in fact, reach high tissue concentrations within the wound of Gustilo–Anderson type II and IIIA open fractures. This may not be true in the more severely compromised and problematic type IIIB injuries because of limitations in blood supply, although this may be irrespective of the antibiotic used.[9]

3.2. Debridement and Irrigation and Local Prophylaxis

Saline is still the most commonly used irrigation solution as it has a track record of reducing infections better than other solutions such as soaps or antimicrobials.[10] That being said, both iodine-based irrigants along with new solutions that disrupt biofilms have shown promise.[11] A broad-spectrum antimicrobial irrigation solution that does not cause host tissue damage would be very beneficial and has been a consistent goal for the medical community. For decades, bone cement has been used as an antibiotic delivery device despite definitive proof of being beneficial.[12] Recently, the orthopaedic trauma community has started to adopt placing vancomycin powder within at-risk wounds, and it has been shown to reduce the infection rates of gram-positive organisms.[13] Since vancomycin does not have much activity against gram negatives, it does not prevent infection from these bacteria and gram-negative bacteria continue to be present in these wounds. The addition of tobramycin to the vancomycin for the gram-negative coverage has shown to be an effective approach,[14] but larger studies are needed to better understand the risk of antibiotic resistance from these approaches.

3.3. Stabilization and Bone Grafts

It is well established that foreign bodies increase the likelihood of infection as they provide a surface for bacteria to adhere and replicate[15] and subsequently form a biofilm. Therefore, the implants that are required to stabilize the bone segments and bone graft that promotes healing actually act as a nidus for infection.[16] Ring fixators and vascularized bone grafts provide the stabilization and aid in fracture union without increasing risk of infection by not introducing implants susceptible to colonization in the wound and by having a vascularized immunocompetent graft instead of an avascular foreign body; unfortunately, these come at much greater expense and increased morbidity. Protecting the foreign body from bacterial colonization by some form of antimicrobial coating, eluting antibiotics, or another strategy until it becomes immunocompetent would reduce chances of infection. Recently, it has been shown that implants may only need to be protected from bacterial colonization for as little as a week, that is, when enough immune cells are found on implants to thwart bacteria introduced to the surface.[17]

3.4. Definitive Closure

Delaying definitive closure of wounds increases the likelihood of infections, but attempting to close a wound too soon can lead to many other problems such as wound dehiscence. This, understandably, often makes surgeons cautious to close too soon leading to more surgeries and greater risk of infection. Promising approaches to use biomarkers for decision support on when to close wounds may allow surgeons to optimize the number of debridements and time closure.[18]

3.5. Preventing and Eradicating Biofilms

Addressing the biofilm challenge is something that needs to occur from the point of injury all way through definitive closure as biofilms allow microbes to become recalcitrant. There are many strategies to both prevent and eradicate them, but perhaps one of the most promising and mature technologies is an antibody that prevents biofilms from forming and eradicates established biofilms. This high-affinity human monoclonal antibody binds to a highly conserved protein that appears to be required by bacteria to form and maintain biofilms. It has demonstrated efficacy in multiple challenging preclinical models along and is currently in early clinical trials.[19,20] A product such as this may prevent bacteria from becoming tolerant to antibiotics or restore their susceptibility and reduce the need for reoperations for implant removal.

4. Local Versus Systemic Antibiotics—New Trends

The use of local antibiotics to the area of interest has expanded significantly in recent years, especially in orthopaedic trauma. The delivery of local antibiotics to the area of concern without the necessity of blood flow to the affected area is of particular benefit in fractures, where localized blood flow is compromised. In addition, the ability to provide large doses that far exceed the minimum inhibitory concentrations (MICs) without the risk of systemic complications associated with intravenous (IV) delivery of antibiotics provides unique benefits to local antibiotic use.

Vancomycin and tobramycin are currently the most commonly used topical antibiotics in orthopaedic trauma. This is typically applied at the time of wound closure directly as powder or mixed with saline as paste. Often, the dose used for vancomycin is 1000 mg or more, while for tobramycin, it is 1200 mg. Importantly, 1000 mg of vancomycin is the same dose that would be provided intravenously for infection prophylaxis while the 1200 mg of tobramycin is 3–4 times higher than the typical IV dose of 5 mg/kg for one-time prophylaxis.

Local vancomycin powder application has been found to be particularly effective in preventing infection after operative treatment of plateau and pilon fractures. The results of the VANCO trial suggested that intrawound vancomycin powder significantly reduced the gram-positive infections in patients with high-risk tibial plateau and pilon fractures, without any observed negative effects. Furthermore, the absolute risk of deep surgical site infection was reduced by 3.4%–4.0%.[21] In a propensity-matched analysis, the use of local vancomycin and tobramycin powder was found to decrease the rate of deep surgical site infections after open treatment of fractures but had no effect on superficial surgical site infections.[14] Conversely, intrawound antibiotic powder was found to have no effect on surgical site infections in open treatment of acetabular fractures.[22]

The primary risks of topical antibiotics concern renal toxicity and nonunion, a risk shared by both vancomycin and tobramycin. In a secondary analysis of the VANCO trial, patients did not have detectable serum levels of vancomycin after 1000 mg used locally in tibial plateau and pilon fractures and none had renal complications.[23] Furthermore, in a retrospective series by Balabanova et al,[24] there was no detectable difference in acute kidney injury between the topical antibiotic and control groups. In a secondary analysis of the PREP-IT trial, cumulative doses of vancomycin were not associated with an increased risk of drug-induced acute kidney injury (AKI) among patients with fracture while the estimated risk of AKI increased substantially to 8% after 4 cumulative doses of 1.2 g of tobramycin.[25] Regarding nonunion, infection is strongly linked to the development of nonunion; thus, preventing infection would directly benefit the success of union after operative treatment. In the VANCO trial, no difference in nonunion rates was noted.[21]

Local antibiotic application has recently taken the form of dissolvable antibiotic beads. The use of calcium sulfate beads impregnated with antibiotics has been used as an alternative for delayed antibiotic elution in infected bones and joints. In a systematic review by Thahir et al, antibiotic-impregnated calcium sulfate (AICS) beads led to total infection remission of 6.8%, which was greater than that of polymethyl methacrylate (21%). Significant complications included wound drainage, which was considerably high in studies involving the treatment of the tibia alone.[26] In the multicenter study by Mereddy et al,[27] the use of local antibiotic-impregnated dissolvable synthetic calcium sulfate beads led to control of infection in 95% of patients. The dissolvable antibiotics have also been used for the treatment of long bone fracture–related infections with intramedullary application. In the study by Patel et al,[28] AICS beads were successfully used in a single-stage treatment protocol for the treatment of long bone fracture–related infection following intramedullary nailing.

Complications surrounding the use of this local antibiotic delivery method have centered on wound drainage and hypercalcemia. In the systematic review by Tarar et al,[29] hypercalcemia was reported in 4.2% of patients, with 0.28% requiring management. Regarding wound drainage, Menon et al[30] recommended careful interpretation of the wound status as 21% of patients developed discharge from the wound at an average of 6 days after inserting the beads.

Systemic antibiotics have been the mainstay of orthopaedic infection treatment. The use of PO over IV antibiotics has recently come in to focus, with the recent oral versus intravenous antibiotics (OVIVA) trial demonstrating noninferiority of oral antibiotic therapy compared with IV antibiotics in the management of complex orthopaedic infections.[31] Intravenous therapy, however, does have the theoretical advantage of achieving peak antibiotic levels rapidly and remains necessary when patients cannot swallow or absorb oral antibiotics. It is important to note that for commonly used antibiotics, the utility in managing infections depends on the period during which levels are above the MIC rather than peak levels. Regarding complications, patients treated with IV antibiotics are susceptible to increased complications, including line issues, decreased patient satisfaction, and longer durations of hospitalization.

The utility of local antibiotics remains complimentary to systemic antibiotic use in the treatment of complex orthopaedic infection management. While the application of local antibiotic delivery devices continues to expand, the role of local antibiotics in isolation in the treatment of orthopaedic infections remains unclear. Systemic antibiotic use remains the mainstay of orthopaedic infection management, with oral antibiotic use coming at the forefront of utility.

5. Conclusion

Orthopaedic implant and fracture-related infections remain a challenging area of clinical focus and active research, but with significant opportunities for new or improved interventions. These new strategies target the eradication of biofilm, with photodynamic therapy and bacteriophage therapy offering promising alternatives to antibiotics. Local antibiotic therapy has continued to evolve, with the use of topical antibiotics in powder form providing a cost-effective therapy to reduce infection risk. The use of antibiotic-impregnated dissolvable beads has also been proposed as a method to treat orthopaedic infections, although the optimal use of this treatment has yet to be elucidated. Finally, improved understanding of systemic antibiotics, both PO and IV, has led to a more judicious and effective strategy to combat infection.

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