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Orthopaedic infections: what have we learned?

Christopher Lee, MD[a,*], Erik Mayer, MD[a], Nicholas Bernthal, MD[a], Joseph Wenke, PhD[b], Robert V. O'Toole, MD[c]

Summary: Orthopaedic infections remain challenging complications to treat, with profound economic impact in addition to patient morbidity. The overall estimates of infection after orthopaedic surgery with internal devices has been estimated at 5%, with hospital costs eight times that of those without fracture-related infections and with significantly poorer functional and pain interference PROMIS scores. Orthopaedic infection interventions have been focused on prevention and treatment options. The creation of new modalities for orthopaedic infection treatment can benefit from the understanding of the temporal relationship between bacterial colonization and host–cell integration, a concept referred to as "the race for the surface." Regarding prevention, host modulation and antibiotic powder use have been explored as viable options to lower infection rates. Orthopaedic infection treatment has additionally continued to evolve, with PO antibiotics demonstrating equivalent efficacy to IV antibiotics for the treatment of orthopaedic infections in recent studies. In conclusion, orthopaedic infections remain difficult clinical dilemmas, although evolving prevention and treatment modalities continue to emerge.

Keywords: orthopaedic, infection, basic science

1. Host Modulation in Infection Prevention

Infection is one of the most devastating and dreaded complications in orthopaedic surgery, often necessitating multiple reoperations and prolonged treatment with systemic antibiotics.[1] Owing to the tremendous negative impact on health and quality of life associated with implant-related infections, attention has increasingly focused on innovative approaches for prevention.[2–8] Despite decades of attempts to optimize antimicrobial prophylaxis, implant sterility, and other exogenous factors, the incidence of infection and resulting revision surgery has continued to rise.[9,10] As a result, there has been a shift in focus in recent years toward host factors that can be identified and modified to medically optimize patients throughout the perioperative period to minimize infectious risk. While medical comorbidities such as diabetes mellitus and obesity are associated with a heightened risk of infection, addressing these factors requires considerable and prolonged efforts. As such, identification of endogenous host factors that can be efficiently and effectively modified perioperatively remains paramount. To that end, we offer a review of some of the exciting work around host physiologic modification to prevent orthopaedic implant-related infections.

1.1. Vitamin D

Recent epidemiological data demonstrate that >65% of patients undergoing arthroplasty are deficient or insufficient in 25-hydroxyvitamin D (25D) and that vitamin D deficiency is directly correlated with the frequency of postoperative implant infection.[11–13] There has also been a plethora of mechanistic work emphasizing the importance of the prohormone 25D as a locally active immune modulator for antigen-activated inflammatory cells mediated through the CYP27B1-hydroxylase pathway.[14,15] This basic science formed the foundation for recent work which demonstrated that 25D deficient animals had logarithmically higher bacterial colonization of implants after surgery and, perhaps most importantly, that deficient animals who were "rescued" with preoperative vitamin D supplementation had infection rates identical to the vitamin D sufficient group.[16] This work promotes a model of safe, inexpensive, and effective immunomodulation before surgery that may improve surgical outcomes by enhancing the immune system's ability to prevent the establishment of pathogenic infection.

1.2. Platelets

Platelets have been shown to possess functionality beyond their well-known role in coagulation, contributing significantly to host antimicrobial defense.[17,18] Indeed, basic science literature has emphasized a link between thrombocytopenia (TCP) and infection, although the clinical magnitude of this effect is difficult to discern.[19,20] In clinical studies, TCP has been associated with poor outcomes after infection.[21–24] However, these studies of TCP lack an ability to assess causation, given that TCP is frequently associated with overall poor health status.[21,24–26] In addition, TCP places patients at risk for postsurgical hematoma formation, which impairs wound healing, provides a nutrient rich environment for bacterial growth that is often shielded from the host immune system, and has been demonstrated to be an

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[a] Department of Orthopaedic Surgery, University of California Los Angeles, Los Angeles, CA, [b] Department of Orthopaedic Surgery and Rehabilitation, University of Texas Medical Branch at Galveston, Galveston, TX; and, [c] Department of Orthopaedic Surgery, University of Maryland, Baltimore, MD.

* Corresponding author. Address: Christopher Lee, MD, University of California Los Angeles Department of Orthopaedic Surgery, 10833 Le Conte Ave, Los Angeles, CA 90095. E-mail: Christopherlee@mednet.ucla.edu

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independent risk factor for infection after orthopaedic surgery.[27–30] A recent study by Greig et al,[31] however, demonstrated that platelet depletion is mechanistically and directly associated with a significantly increased infectious burden that was both dose-dependent and reversible. As such, these findings not only validate the relationship between platelet levels and infectious burden in a well-validated mouse model of PJI but also establish direct causation through a series of mechanistic ex vivo experiments. In addition, this study demonstrates both the magnitude and the modifiability of this phenomenon.

1.3. Neutrophils

Another exciting area of research has been the identification of a role of human neutrophils as a potential "guardian" of the surface of implanted devices. Ghimire et al have demonstrated in vitro and in vivo that neutrophils can patrol the surface of implanted biomaterials and phagocytize bacteria. The work demonstrates both the impact of concentration—neutrophils cleared implants from colonization only when the neutrophil:bacteria was greater than 1—and the importance of time—neutrophils were no longer successful at clearing the implant if the bacteria had a 3-hour head start on the implant.[32] Furthermore, it highlights mechanistically how the immune system can serve to protect orthopaedic implants from bacterial colonization and identify some of the factors that may tip the balance of this relationship in either direction.

1.4. Summary

Despite decades of work, orthopaedic implant infections continue to wreak disastrous complications on even the best surgical operations. Our efforts to increase operating theater sterility and increase local antimicrobial concentrations have improved outcomes but not to the degree we would have hoped. It is our belief that a successful host immune system is likely the most reliable chaperone of the orthopaedic implant, and higher rates of complication and poor outcomes can be anticipated in hosts with compromised immune systems. Thus, the corollary is likely true, enhanced immune systems likely would protect implants and patients from postoperative infection far more robustly and agnostically than many of our "targeted" antimicrobials. Whether it is leveraging the vitamin receptor on antigen-activated inflammatory cells, repleting platelets to ensure adequate concentrations of platelet-derived antimicrobials, or activating the neutrophils to achieve site-specific bacterial clearance, the host immune system offers us a plethora of mechanisms and potential targets to improve surgical outcomes.

2. Timeline and Participants in "the Race for the Surface"

The "race for the surface" concept has been the key explanation for understanding competition between bacterial colonization and host–cell integration to protect implants from infection.[33,34] If microbes reach the surface first, they can attach, replicate, reach a quorum, form a biofilm, and cause a recalcitrant infection. Conversely, host–cell integration occurring before bacteria colonization will result in lower chances of infection and improved implant survival. In this concept, the fate of the implant hinges on which cells reach the surface of the implant first.

A very common anti-infection strategy is to protect the implants against bacterial colonization by an active coating (antimicrobial released to kill nearby microbes), but the timeline for the host to be able to fend for itself is still unknown. Therefore, the optimum antimicrobial release kinetics and duration are unknown. Because this key information remains elusive, researchers and clinicians are tend toward caution and often aim for extended release therapy, sometimes a month or more. Recently, a preclinical implant infection model was developed where the device implantation was uncoupled from bacterial challenge to provide an understanding of the temporal cellular events that are required to prevent implant infection.[35] In this bilateral intramedullary nail rat model, *Staphylococcus aureus* was injected into the tail vein either immediately after or 1, 3, and 7 days after implant placement. Two weeks after inoculation, implants and tissues were harvested for bacterial enumeration. As time between implant placement and bacterial challenge increased, infection rate and bioburden decreased substantially. Most of the implants had measurable bioburden when challenged at day 1, but only one implant had recoverable bacteria when inoculated 7 days after placement. Approximately one-third of the implants had recoverable bacteria when challenged 3 days after placement. In addition, to understand the time course of host integration and which cells offer protection, the implants were placed in the femoral canals of a group of uninoculated animals. These animals were euthanized at 1, 3, or 7 days, and the host cells adhered to the implant were identified using flow cytometry. Interestingly, and as anticipated, the protection against infection corresponded to a shift in host cell population surrounding the implant. Initially, cells present were primarily nondifferentiated cells, such as bone marrow mesenchymal stem cells or immature hematopoietic cells. At day 3, there were some mature monocyte/macrophage cells, and a robust mature population was present on day 7.

Importantly, it seems that the initial cell population differentiated into the immune cells and that the timeline for this seems to be fairly conserved across species. The types of cells that initially attach to implants are consistent across species, from rodent to nonhuman primates.[36,37] In addition, in vitro cellular differentiation of both rodent and human hematopoietic precursors occurs over similar time frames, differentiating within 3 days after stimulation, as was also seen in the present in vivo study.[38–40] This suggests that the timeline for host protection in humans may be similar and relevant for patients. Studies in different anatomic locations, species, and health status (comorbidities such as diabetes, advanced age, trauma, etc.) along with investigation of implant coatings and antimicrobial release patterns will help to clarify further the timeline required for the body to protect the implant and surrounding tissue against infections. Taken together, it seems that future therapies and strategies may only need to protect implants against bacterial colonization for approximately 1 week.

3. PO Versus IV Antibiotics in Orthopaedic Infections

The mainstay of orthopaedic infection treatment has traditionally been a combination of surgical debridement and intravenous antibiotics. The preference for intravenous antibiotics over oral therapy as standard of care has long been perpetuated, and this dogma may be more a function of the temporal progression of antibiotic discovery. Salvasaran was the first antibiotic to be routinely used, requiring multiple parenteral injections. Similarly, protonsil was the first antibiotic to be used against Streptococcus and Staphylococcus and was given intramuscularly. In 1970, the influential article by Waldvogel et al[41] on the treatment of osteomyelitis suggested 4 to 6 weeks of parenteral antibiotic therapy as a necessity. However, no large single randomized controlled trial (RCT) has demonstrated superiority with

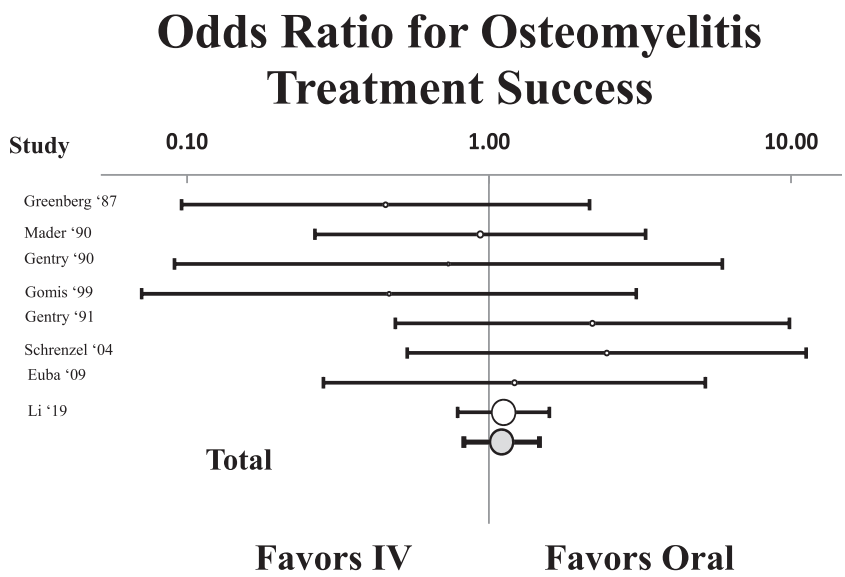

Figure 1. Forest plot displaying efficacy of oral versus intravenous antibiotics for treatment of osteomyelitis. None of the highlighted studies have shown superiority of one treatment modality over the other. Note: The circle size represents the relative weight of an individual study's odds ratio within the overall meta-analysis, which is based on sample size and power analysis. The combined odds ratios are depicted by the shaded circle.

intravenous treatment over oral treatment. Regarding the treatment of osteomyelitis, eight studies have shown no difference in treatment success when comparing intravenous versus oral antibiotic therapy (Fig. 1).[42–49] In the RCT by Li et al,[46] 1054 patients were treated with intravenous versus oral therapy during the first 6 weeks for complex orthopaedic infections, and oral therapy remained noninferior to intravenous as assessed by treatment failure at 1 year

Intravenous therapy, however, does have the theoretical advantage of rapidly achieving peak antibiotic levels and remains necessary when patients cannot swallow or absorb oral antibiotics. However, for commonly used antibiotics such as beta-lactams, glycopeptides, or macrolides, antimicrobial function is dependent on the period of time during which levels are above the minimum inhibitory concentration (MIC), rather than peak levels. Exceptions to this are aminoglycosides and quinolones, in which effectiveness is related to peak concentration levels. Regarding complications, in the largest RCT comparing IV versus PO, the patients in the IV arm had significantly more adverse events including line complications, decreased patient satisfaction, and longer durations of hospitalization.

Regarding duration of antibiotic therapy, treatment durations are unfortunately based primarily on tradition, rather than comparative studies. For osteomyelitis, recommendations were originally made before the 1960s, when antibiotics and surgical techniques significantly differed from current practices. In comparing osteomyelitis treatment, 2 RCTs showed noninferiority between short (mean 43 days) versus long (mean 84 days) treatment durations.[50,51] This has also been observed when comparing treatment for cellulitis, osteomyelitis with removed hardware, diabetic osteomyelitis, septic arthritis, and nonorthopaedic infections including pyelonephritis and intra-abdominal infections (Fig. 2).

In summary, oral antibiotic therapy for the treatment of orthopaedic infections has continued to gain in popularity. Further studies are still needed to better define the optimal length of therapy, although recent studies have suggested noninferiority between shorter and longer durations.

4. Antibitiotic Powder Use in Orthopaedic Infection Prevention—Current Concepts

4.1. Rationale and Current Use

The clinical use of topical antibiotics to prevent surgical site infections dates back at least World War II with the use of sulfa powder. The rationale for their use is particularly strong in orthopaedic trauma. Local antibiotics are delivered to the area of interest without concern for localized blood flow compromise that may accompany open and closed fractures and prevent IV antibiotics from reaching the surgical site. Furthermore, the much larger local doses used in topical antibiotics are believed to easily exceed MICs without as much risk of systemic complications as intravenous delivery of antibiotics.

Vancomycin and tobramycin are currently the most used topical antibiotics in orthopaedic trauma. Orthopaedic trauma surgeons are very familiar with the use of these 2 antibiotics in the form of antibiotic beads, which has had widespread use in open fracture wound management for many decades. Antibiotic powder is typically applied at the time of wound closure either directly as a powder or mixed with saline as a paste. Vancomycin powder is the most commonly used given its activity against gram-positive pathogens and its low cost. The typical dose is 1000 mg or more. Some surgeons add tobramycin for its gram-negative activity, and 1200 mg is a typical dose. It should be noted that while 1000 mg of vancomycin is the same dose that would be administered intravenously for infection prophylaxis, the 1200 mg dose of tobramycin is 3–4 times higher than the typical IV dose of 5 mg/kg for one-time prophylaxis.

4.2. Efficacy in Spine and Arthroplasty

The first substantive work examining the efficacy of topical antibiotics to prevent surgical site infection began in the spine and arthroplasty literature. Despite the limitations of these studies, with relatively few RCTs and strong reliance on mostly retrospective data, a very consistent picture in favor of their use

DIAGNOSIS	SHORT (days)	LONG (days)	RESULT	#RCTs
Cellulitis	5-6	10	Equal	4
Osteomyelitis	43	84	Equal	2
Osteomyelitis with removed Hardware	28	42	Equal	1
Diabetic Osteomyelitis, debrided	10-21	42-90	Equal	2
Septic Arthritis	14	28	Equal	1
CAP	3-5	5-14	Equal	12
Pyelonephritis	5 or 7	10 or 14	Equal	7
Intra-abdominal infection	4	10	Equal	2
GNR bacteremia	7	14	Equal	2

Figure 2. There has been no difference in efficacy regarding infection eradication over multiple randomized controlled trials of antibiotics comparing short versus long treatment durations for varying infectious pathologies. CAP, community acquired pneumonia. GNR, gram-negative rod.

has emerged, leading to an increasing interest for their use in orthopaedic trauma.

In contrast to spine and arthroplasty literature, the retrospective studies to date have shown a more mixed picture, but there is one large RCT supporting the practice.[52,53] Some retrospective studies have demonstrated benefit of topical powder in preventing infection, and others no effect.[54–59] These studies vary in the size of the treatment group, the type of fractures included, and the type of powder used. To date, there are no meta-analyses combining these studies.

However, unlike in spine and arthroplasty, there is a well-powered, large, multicenter RCT. The VANCO trial randomized 980 patients to either 1000 mg vancomycin powder at wound closer or a control group.[53] The study used 2 primary outcomes using different analysis techniques that both yielded approximately 35% reduction in infection overall (P values of 0.04 and 0.06). A post hoc analysis examining only gram-positive infections, the primary target of vancomycin, demonstrated a 50% reduction in deep infections ($P = 0.02$).

4.3. Safety

The main safety concern regarding topical antibiotics is the risk of renal toxicity, a risk shared by both vancomycin and tobramycin. It would not be anticipated that doses of vancomycin near 1000 mg as a one-time dose would be at particular risk because this is the same dose that is routinely given IV twice a day for many weeks. There are several relatively reassuring studies in spine, arthroplasty, and other specialties demonstrating acceptable serum levels and no concern for renal toxicity. A secondary study of the VANCO trial also demonstrated that no patient had detectable serum levels of vancomycin after 1000 mg used topically in tibial plateau and pilon fractures, nor did any patients suffer renal complications.[60]

There is much less information regarding tobramycin powder, although tobramycin has been used for decades in antibiotic beads. Two retrospective studies examining vancomycin and tobramycin found no reason for concern.[55,58] While a recent secondary analysis of a RCT found no increase in nephrotoxicity with cumulative dosing of topical vancomycin, there was a substantially increased risk of acute kidney injury (8%) after more than 3 doses of 1.2g tobramycin.[61]

A second concern is the potential for selecting out antibiotic-resistant organisms. This issue is of course a theoretical concern with the use of any antibiotics but is more of a possibility with long duration of low doses of antibiotics below the MIC. Topical antibiotics are therefore theoretically less likely to be of concern given the very short duration of exposure and relatively high dose. This issue has not had much investigation yet, but the VANCO substudy presented at the 2019 annual meeting of the Orthopaedic Trauma Association (OTA/AO) on this topic demonstrated no concerning pathogens.[62] The authors presented a decrease in infections because of gram-positive pathogens as expected and no change in gram-negative infections. No unusual pathogens were observed. No similar work exists to our knowledge examining the effect of tobramycin powder alone on the potential for antibiotic-resistant pathogens. However, encouraging data from the 2021 OTA/AO annual meeting found that in retrospective cohort study of patients with open fracture, there was no increase in antibiotic resistance for those administered a combination of topical vancomycin and tobramycin compared with those who received no local antibiotics.[63]

A final safety concern is nonunion because both vancomycin and tobramycin have cytotoxic effects on osteocytes at high doses. Infection is a strong driver of nonunion, so any technique that reduces infection would tend to benefit union. The VANCO trial is reassuring because it demonstrated no differences in nonunion rates, although one limitation is the primary outcome was only at 6 months.[53] This issue has not yet been well investigated in longer-term studies.

4.4. Summary

Topical antibiotics are a promising technique to prevent surgical site infection. Retrospective data in spine and arthroplasty have

demonstrated efficacy. Retrospective data from orthopaedic trauma studies have demonstrated more mixed results, but the VANCO trial convincingly demonstrated a 50% reduction ($P = 0.02$) in gram-positive infections. There do not yet seem to be concerns demonstrated with renal toxicity, bacteria resistance, or nonunion with topical vancomycin, but further work is still needed on these topics. Little work has been performed to date regarding tobramycin powder as a potential adjunct to target gram-negative infections, but studies are underway and the early results are reassuring.

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 aim to (1) fortify individual patient physiology against infection, (2) improve treatment options for those with active infections, and (3) prevent infection at the time of surgery. Investigations into direct host physiologic modifications through immune pathway modulation represent enticing targets for novel therapeutics or low-cost supplementation (eg, vitamin D). Meanwhile, elucidating the efficacy of existing therapies, such as evaluating the necessity of IV antibiotics (in comparison with PO medication), potentially reduces the clinical burden of treating orthopaedic infections for patients. Finally, improved understanding of the role of prophylactic topical antibiotic therapies offers another potential weapon in our surgical armamentarium in the fight against infection.

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