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CORR Insights®: Blended Chitosan Paste for Infection Prevention: Preliminary and Preclinical Evaluations

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Where Are We Now?

Orthopaedic infections are a challenging issue for both caregivers and patients. A former colleague who specializes in caring for patients with implant-related infections once told me that his patients undergo an average of six to eight surgeries before their first meeting. First-line management of this

condition when it presents acutely might consist of irrigation and débridement, accompanied by the exchange of any modular elements of the implant, and administration of intravenous antimicrobials. Unfortunately, implant infections are characterized by the presence of drug-resistant biofilms, which can survive treatment by intravenous antibiotics. Common microbes typically encountered include *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Propionibacterium acnes*. Most of these microbes can be killed by gentamicin, vancomycin, or cefazolin, among other drugs, but require high concentrations and long exposure times.

Many practitioners suspect that patient health plays a role in how susceptible a patient might be to infection [2], but large studies do not

always control for patient age or immune status. We do know, however, that patients of advanced age or poor health status tend to be more susceptible to orthopaedic infection, and may not respond as well to treatment.

Multimodal management of this complex condition is important. Local antimicrobials, while capable of achieving concentrations thousands of times higher than systemic antimicrobials with minimal complications, must reach the biofilms to be effective. Anyone who has seen the débridement of infected granulation tissue is aware that there are major transport barriers to the distribution of antimicrobials in an infected wound. Only after definitive débridement can local antimicrobials be relied upon to scour the wound for residual disease and promote the return of healthy tissue.

Engineers and clinicians have sought to protect the surfaces of implants with low-dose delivery vehicles for several decades [3, 5]. It is difficult to assess the clinical efficacy of these prophylactic treatments due to low primary-infection rates. When fluid is leaving the wound bed via

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circulation and lymphatic uptake, low-dose depots are unlikely to maintain concentrations likely to kill biofilm for long enough to be effective due to fluid exchange. However, if there are planktonic bacteria in the wound, these treatments may help to lower the overall bacterial load, and may help the body's own immune system prevent an infection from occurring.

Studies differ on the effectiveness of local delivery, both for prophylaxis and treatment [1, 4]. This controversy stems from differences in host health status, low primary-infection rates, differences in débridement techniques, and differences in antimicrobial susceptibility of the infections to the selected agents. Managing infections requires clinicians and microbiologists to understand transport from engineers, engineers and microbiologists to understand bacterial physiology from clinicians, and both clinicians and engineers to have a grasp of microbial behavior and susceptibility from microbiologists (in addition to the biomechanical issues which accompany débridement, joint replacement, and reconstruction). It is therefore unsurprising that so much controversy remains in this field.

Where Do We Need To Go?

Local delivery can be achieved in a number of ways. Clinicians sprinkle

free antibiotics into the wound, mix antimicrobials into morselized cancellous bone graft, or mix it in bone cement to provide local antimicrobials to an infected wound. Bone cement is used either in a bead pouch as small spheres, or formed into an implant shape by hand, known as an “antimicrobial loaded spacer.” There are many different local antimicrobial depots under development by both labs and corporations across the country. Chitosan is desirable because it's generally regarded as safe [6], making its transition to market easier than less traditional, more-engineered polymers. However, chitosan's degradation rate is relatively slower than might be desired, and is mostly dependent on wound pH. Chitosan is limited in its ability to modify the rate at which antimicrobials are released once they contact the water. This is because chitosan is a sugar and sugar chemistry is more limited and challenging than traditional polymer chemistry. Other engineered materials may have a wider range of adjustable properties, but they also are made from novel polymers, and require much more extensive and expensive preclinical work before they might see clinical use. The current work, therefore, represents an initial bench-top effort to develop and validate a release system for the management of orthopaedic infection. Chitosan and other soft/polymeric materials have great

promise for providing infection management and prevention in the surgical environment, and every effort should be made to bring a high-dose material to market for orthopaedic use.

Berretta and colleagues report on the degradation rate, biocompatibility, and release properties of their depot in bench-top work as a first step in presenting this new chitosan formulation. The authors also provide a mouse infection prevention model to show proof of concept and efficacy. Interpretation of animal infection prevention models is challenging, as young healthy animals will frequently beat infections on their own without antimicrobial therapy, and the cost of animal research means that an investigator can never power their groups well enough to determine if the effect is “real” or an artifact of an unseen confounder like animal health (typically groups are on the order of eight to 10 animals). The proof of efficacy for any depot device will likely be in human trials, once the depot is used to accompany the débridement and treatment of infections in a referral center. The current work appears to have met the goals of providing adequate release to manage a biofilm, and provide reasonable compatibility and degradation rates. The next steps would be larger animal models that are closer to the intended human use of this material, and studying how it

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might best be used in orthopaedic wounds without interfering with the devices themselves. It is unlikely that the chitosan material will be strong enough to provide a structural spacer, a technique similar to a bead pouch might be desirable.

How Do We Get There?

Proving the clinical efficacy of local antimicrobial depots will be a challenge. Before the FDA can approve a depot made available to clinicians for routine use, the device will need a specified formulation in terms of its antimicrobial load. Funding agencies should support a clinical trial with a high-dose antimicrobial in an infection-control model coupled with débridement to show, in my view, the considerable benefits of this treatment. Some researchers studying local delivery, however, are somewhat skeptical of its value [8], and while some clinical trials have found strong effects [1], others have not [4]. Because infections are relatively rare, powering clinical trials to show efficacy in treating them is difficult. While some centers are showing effectiveness in human and animal trials with the sprinkling of vancomycin [7] and other antimicrobials in wounds, some of this efficacy is likely related to augmenting the subjects' own immune systems, variability

in the location of the disease and placement of the depot, and the extent of débridement in each case.

Multicenter clinical trials will not show the necessary efficacy unless the standards and instructions for débridement are rigorously disseminated at the beginning of the trial, and adhered to throughout. Antimicrobials are not likely to penetrate far into infected granulation tissue that remains after a poor débridement. Future clinical trials should seek to provide definitive treatment options for implant infections when combined with débridement. The selection of a vehicle like chitosan, with a relatively easy regulatory pathway, might be desirable for commercial development of these high-dose depots. This material would lower the cost and risk associated with a company entering this controversial marketplace. The generation of a successful clinical infection trial, with major reduction in the associated infection rate, would be a major step on the road to getting these materials approved by the FDA and available for use.

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