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MEETING REPORT

ORS 2012: session 45—orthopaedic infection

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Meeting Report from the Orthopaedic Research Society 2012 Annual Meeting, San Francisco, CA, USA, 4–7 February 2012.

Propelled by the growing popularity of total joint replacements and the emergence of antibiotic-resistant strains of common bacteria, the gravity and expense of implant-associated orthopedic infections has become a significant concern. For patients, these infections are the shattered promise of renewed mobility, potentially leading to a wheelchair-bound life and sometimes amputation. For orthopedic surgeons, these infections are an unwelcome risk and a huge complication to high-quality patient care. For hospital administrators and insurers implant-associated infections have become an economic burden, often exceeding $60 000 per patient.[1]

Efforts directed at reducing the opportunity for infection by controlling the surgical environment have brought infection rates down to about 1%,[2] but with more than a million total joint replacements per year in the USA, the number of patients with infected implants is in the tens of thousands.[3]

If the combination of the surgical suite and the patient cannot be made perfectly aseptic, then new tools need to be created to prevent the remaining 1% of infections from becoming established. Two broad categories of these new tools were presented in Session 45: (i) schemes for the controlled release of antimicrobials at the site of an orthopedic implant and (ii) novel localized or systemic prophylactic or therapeutic agents.

Controlled Release of Antimicrobials at the Site of an Orthopedic Implant

The primary focus has been on prevention of infection in the frank recognition that therapeutic intervention targeting infections established in biofilms is extremely difficult.[4] Numerous avenues are being explored that generally involve some matrix that can be co-administered with the implant and can serve as a depot for the sustained release of an antimicrobial agent. Generally, attractive features for such matrices are: (i) non-interference with the growth of bone into the implant; (ii) little or no impact on the surgical procedure; (iii) pre-cast or cast in-place; (iv) mechanical stability if permanent or resorbable if not; (v) controlled release of the antimicrobial agent.

Four of the nine presentations in this session were explicitly aimed at the design or evaluation of matrices and antimicrobial agents. Jim Odekerken, Tim Welting and colleagues from the University of Maastricht Medical Center presented a new rabbit model of intramedullary orthopedic infection for the evaluation of antimicrobial coatings on titanium substrates.[5] Essentially, a hole was drilled down the tibia; contaminating *Staphylococcus aureus* (3.8×10^5 cfu) were introduced in suspension followed by a model titanium 'implant' and the hole was sealed. Over the 6-week time course, infections were observed by monitoring: (i) animal weight, (ii) markers of inflammation, (iii) radiographic imaging of cortical thickening, bone remodeling and osteolysis, (iv) ^{18}F-FDG micro-positron-emission tomography imaging for detection of infection *in vivo* and (v) culture of the infecting organism from the tibia. Each measure yielded predicted changes that were absent in non-infected controls. None of the infected rabbits resolved the infection. The authors now believe they have a robust system for testing antimicrobial coatings applied pre-surgically to the model implant.

A related experimental system featured the insertion into a sheep femur of a porous titanium plug that served as the model implant, the vehicle for contaminating bacteria and the source for the experimental antimicrobial cationic steroidal antimicrobial 13 (CSA-13). Kristofer Sinclair and his colleagues at the University of Utah have developed an ovine model to test the ability of CSA-13 incorporated into and released from an implant-associated silicon polymer layer to prevent infection by a high dose of methicillin-resistant *S. aureus* (MRSA).[6] Control animals were infected so severely that euthanasia was required. In contrast, CSA-13-treated sheep displayed no signs of infection by radiographic, histologic or microbiological measures. CSA-13 is derived from the novel class of ceragenins, synthetic membrane-active antimicrobials built on a steroid backbone.[7] One of the attractions of CSA-13 is its toxicity for Gram-positive and Gram-negative bacteria as well as strains resistant to conventional antibiotics.

The broad-scale antimicrobial activity of silver ion has made it an attractive antimicrobial candidate for incorporation into pre-coated implants. A new scheme for incorporating silver directly into bioactive orthopedic bone substitutes such as hydroxyapatite, biphasic calcium phosphate and bone-like mineral (BLM) coatings was presented by Jae Sung Lee and William Murphy of the University of Wisconsin.[8] Their two-step procedure began with pretreatment of BLM with sodium citrate followed by incubation with silver nitrate, yielding BLM

studded with nanocrystals of silver (Ag^0) that had slow and linear release rates for silver ion (Ag^+) in water over periods of days to weeks. They observed a marked dependence on the quality (biphasic vs linear) and rate of Ag^+ release on the levels of citrate and silver nitrate used in the preparative steps.

In another approach, Jessica Jennings and her colleagues from the University of Memphis[9] presented early work on the development of a matrix for the delivery of *cis*-2-decenoic acid (C2DA), a fatty acid that has been observed to prevent the formation of new biofilms and disrupt pre-existing ones.[10] Using pre-formed, biodegradable chitosan sponges and PEG-400 as a co-solvent, they were able to make a delivery system that could release levels of C2DA reported to inhibit the formation of biofilms for at least 2 weeks.

Novel Localized or Systemic Prophylactic or Therapeutic Agents

Three presentations featured potential therapeutic agents that could be administered systemically or at the site of surgery. Platelet-rich plasma (PRP) has been observed to promote tissue and bone healing.[11] Hongshuai Li and colleagues asked whether PRP might have antimicrobial activities as well.[12] PRP exhibited a modest and short-lived apparent reduction in the growth of methicillin-sensitive *S. aureus* (MSSA) and MRSA, and Group A *Streptococci*, but had no effect on *Escherichia coli* or *Pseudomonas*. Bacterial burdens near sites challenged with MSSA in implant-associated transvertebral rabbit model were modestly reduced in PRP-treated animals compared with saline-treated controls.

Infecting bacteria severely reduce the impact of conventional antibiotics by forming biofilms and by acquiring resistance genes. One way to enhance the clinical efficacy of available antibiotics may be by finding synergies with other therapeutic modalities. Sana Dastgheyb and her colleagues at Thomas Jefferson University looked for potent combinations of antibiotics with photodynamic therapy.[13] In the presence of light and sub-minimum inhibitory concentration levels of the protein synthesis inhibitors tobramycin and chloramphenicol, the photosensitizing porphyrin meso-tetra(4-aminophenyl)porphine caused a 3–3.5 log decrease in the growth of *S. aureus* suspension cultures. A smaller 1–1.5 log decrease was observed with the cell wall synthesis inhibitors vancomycin and ceftriaxone. The impact of antibiotic/photodynamic therapy combinations on *S. aureus* biofilms and schemes for delivery of the two drugs plus light are surely in these investigators' minds.

The ability to passively immunize patients against *S. aureus* infections could significantly reduce the impact of contaminated total joint replacements many of which are infected with MRSA. John Varrone and his colleagues at the University of Rochester Medical Center have prepared monoclonal antibodies against glucosaminidase (Gmd), a cell wall-modifying enzyme that elicited high levels of IgG antibodies in mice that had overcome experimental infection with *S. aureus*.[14] One monoclonal antibody inhibited Gmd enzyme activity, recognized Gmd from the majority of MSSA and MRSA strains, and forced *S. aureus* to grow in gigantic clusters *in vitro*, but it had only modest effect on the progress of experimental infections in a murine transtibial osteomyelitis model.[15]

Sequelae of Orthopedic Infections: Deep-tissue Infection and Implant Corrosion

Finally, two presentations addressed peripheral but relevant issues for orthopedic infections. Mara Schenker and her colleagues from the University of Pennsylvania created a model for deep soft-tissue infections.[16] Bioluminescent *S. aureus* were introduced into an absorbable gelatin sponge and placed into a deep incision in the thigh muscle so that it was juxtaposed to the femur of a C57Bl/6 mouse. Bioluminescence, body temperature, animal behavior, wound appearance and bacteremia (in some animals) all indicated successful establishment of infection by 72 h. These investigators plan to use this model to assess the impact of early interventions in the management of deep wounds.

What impact do infections have on the corrosion of orthopedic implants? Mathew T. Mathew and his colleagues from Rush University Medical Center measured the contribution of bacterial lipopolysaccharide (LPS) to corrosion in metal prostheses.[17] Microscopic and electrochemical measures of corrosion of CoCrMo alloys in the presence of bovine calf serum and various concentrations of *E. coli* LPS demonstrated that slightly accelerated corrosion definitely occurred at low concentrations but that high levels of LPS reduced the level of corrosion possibly by adsorption of protein and LPS on the metal surface.

Most of the work presented in Session 45 were at a very early stage. One hopes that several of these new approaches will be pushed to the clinic in the near future.

Conflict of Interest

Dr Daiss was a half-time consultant with Codevax, Inc. from 1 September 2010 to 31 January 2012.

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