Active immunization with and without antibiotics in the prevention of biomaterial centered infection

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Summary of Background Data
Total knee arthroplasty (TKA) is a common operation in the United States. Recent infections have been estimated to occur in 0.39 - 2% of primary TKA and as high as 6.7% in revision surgeries. *Staphylococcus aureus* is the most common infecting organism. Over the past 10 years, infections with strains of methicillin-resistant *S. aureus* (MRSA) are becoming more frequent. The end results of surgical treatment of infected TKA are often poor with the success rate being as low as 18% for MRSA infections in comparison to 89% for non-resistant organisms. The vaccine (StaphVax®, Nabi, Rockville, MD) is composed of *S. aureus* type 5 and 8 capsular polysaccharides conjugated to an equal weight of recombinant exoprotein A, and has previously been demonstrated to confer protection against *S. aureus* bacteremia in end-stage renal disease patients on hemodialysis.

Study Design
Our novel rabbit knee implant model was employed to study the additive and possibly synergistic protective effect of a vaccine against *S. aureus* in the presence of antibiotic prophylaxis using MRSA as the infecting organism.

Objective
To demonstrate the efficacy of a *S. aureus* vaccine in combination with standard antibiotic prophylaxis in preventing MRSA biomaterial-centered infection in a rabbit knee implant model.

Methods
Fourty-four mature New Zealand White rabbits were used in this study. Twenty-two animals were vaccinated with 50mcg of StaphVax® 49, 28 and 7 days prior to surgery. Twenty-two controls, or non-vaccinated animals, were administered with saline instead of vaccine on the same days prior to surgery. These groups were then subdivided into groups that receive antibiotic prophylaxis, 50µg/kg of ceftriaxone, and those that did not receive antibiotic prophylaxis. This yielded a total of four groups: 1) control group which received no treatment 2) vaccine control group which received vaccine alone 3) antibiotic control group which received antibiotics alone 4) experimental group which received the combined therapy of antibiotics and *S. aureus* vaccine. Each group comprised of 11 rabbits (22 surgical knees). Antibody titers were obtained on the days of vaccination and at the time of surgery to determine immunization effectiveness.

The surgical procedure was performed as follows. After administration of anesthesia, a lateral arthrotomy was made under sterile conditions exposing each lateral femoral condyle. A 3.5mm diameter hole was drilled into the lateral femoral condyle, doughty polymethylmethacrylate (PMMA) cement (Osteobond, Zimmer Inc., IN) was injected into the defect, followed by the insertion of a 15mm long 3.5mm stainless-steel cannulated screw with an ultra-high molecular weight polyethylene (UHMWPE) washer.

After closure of the joint capsule, one knee was challenged with a target inoculum of 1*10^6 colony-forming units (CFU) of MRSA (strain STO21) and the contralateral knee challenged with a target inoculum of 2*10^6 CFU MRSA in a blinded fashion. Animals were sacrificed after seven days, and biopsies of five sites in each knee were obtained to evaluate for biomaterial-centered infection (synovial fluid, fascia, necrotic tissue, bone and biomaterials). Each knee was visually evaluated and graded for the intensity of the infection. Biomaterial growths from the implant surfaces and surrounding tissues were quantified. A blood sample, liver and kidney biopsies were also tested for infection. Biomaterial centered infection was considered positive when MRSA was present in bone or on the screw/washer implant in addition to two other tissue samples from the same knee. Isolated bacterial growth in the soft tissues without growth at the implant or bone was regarded as a negative result. Along with detecting bacterial growth in tissue and material samples, blood samples were also taken to measure erythrocyte sedimentation rates as an inflammatory marker for infection.

Results
Vaccine titers of specific IgG on the day of surgery ranged from 28.9 to 117.5 mcg/mL, with a median of 68.9mcg/mL, and a mean 71.8 mcg/mL (SD 30).

The protective effect of vaccination against *S. aureus* was detectable in individual tissues when the knee joint was challenged with MRSA. Infection and Sedimentation rates were as follows: the control group, 73% (16 of 22 knees) ESR 34.1, vaccine controls group 55% (12 of 22 knees) ESR 11, antibiotic control group 18% (4 of 22 knees) ESR 6.2, and experimental combine treatment group (2 of 22 knees) ESR 4.7.

Discussion
Our rabbit knee model utilizes commonly employed orthopaedic implant materials in an intra-articular *in vivo* milieu and provides an effective method for the evaluation and treatment of biomaterial-centered infections. With the growing prevalence of antibiotic resistant organisms, active immunization may be a promising anti-infective strategy. This may be particularly true for the subset of patients who require greater protection than antibiotic prophylaxis can provide. Patients with diseases such as rheumatoid arthritis and diabetes may fall in this category as well as other immuno-compromised states. Also patients undergoing revision total joint arthroplasty may have benefit from such treatment as well as patients who have a know history of MRSA infection. Our results demonstrate that in our rabbit model, the combined therapy of antibiotics with *S. aureus* vaccination conveys an additive and perhaps synergistic protective effect against biomaterial-centered MRSA infection. We believe that novel therapies in combination with standard antibiotic prophylaxis will help reduce rates of infection in certain population subsets. As the number of total joint procedures increases each year along with the prevalence of resistant infections, the goal to derive new antimicrobial treatment modalities has paramount importance.