Development of Pre-Clinical In Vivo Models to Assess the Efficacy of Antimicrobial Products to Reduce Device-Related Infections

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Statement of Purpose: Device-related infections and associated microbial biofilm formation on implanted devices represent a significant clinical problem, which remains the most common serious complication of medical devices. Once established, these infections prove difficult to effectively treat with existing antibiotic regimens. Several new products are being developed aimed at incorporating antimicrobial drugs and biomaterials as a component of the implanted device itself to provide infection control at the implant site. While several in vitro antimicrobial test methods have been established, clinically relevant demonstration of antimicrobial product efficacy ultimately requires animal models of implant infections in which a consistent, but non-lethal, implant infection is established. In response to the need to test the efficacy of several anti-microbial products under development, we have developed animal models of device-related infections using numerous clinically relevant bacterial strains to test a wide array of antimicrobial products. Because device-related infections can occur within a variety of implant sites, animal models of several different implant locations have been developed. This presentation will provide a review and discussion of the development of these animal models.

Methods: In order to develop methods to provide consistent, reproducible, and quantitative data for assessing the efficacy of antimicrobial components of medical devices, several experimental variables were examined: implant site, bacterial strain, method of inoculum delivery, device type/material, and methods for quantitative microbial recovery from explanted devices. Because many of the test results may ultimately be used in regulatory submissions for efficacy claims, it was important to utilize implant sites that are clinically relevant to the expected clinical use of the final product. Such implant sites used in these studies include subcutaneous implants, bone defects to establish osteomyelitis, and abdominal muscle defects or intraperitoneal implant sites to assess hernia repair materials. While most studies were performed in rabbits, subcutaneous and hernia repair models were also evaluated in rats.

The bacterial strains that are most commonly found in clinical device infections can vary depending on the device and implant site. The use of strains that are clinically relevant for each particular device and clinical use is thus important. The ability to create subcutaneous implant infections using several different strains was thus evaluated. The strains used included: *Staphylococcus aureus* (methicillin-sensitive and –resistant), *Staphylococcus epidermidis*, *Staphylococcus capitis*, *Staphylococcus lugdenensis*, *Escherchia coli*, *Propionibacterium acnes,* and *Acinetobacter baumannii*. Additional strains were evaluated in different implant sites, including *Enterobacter aerogenes* and *Enterococcus faecalis*.

Finally, the use of sonication has been reported as an efficient method to remove adherent microbes from implanted materials (e.g., Tollefson et al, Arch Surg. 1987; 122(1): 38-43). Single versus multiple sonications were evaluated to determine recovery efficiency of microbes from explanted devices.

Results: Successful implant infections were established at each implant site. A comparison of results using different bacterial strains, different implant sites, and different test article compositions indicate great variation in the bacterial dose required to establish consistent infections under these different conditions. Results indicate that the development and severity of infection are dependent on different device geometries or surface characteristics, as well as different bacterial strains. In studies in which an infection is established in a device-implant pocket, a biofilm-like infection is effectively created on the implanted device. Device sonication yielded significant microbial recovery, but with reduced number of microbes with each subsequent sonication, though fully exhaustive removal was not achieved. The use of antimicrobial coatings or covers around the implanted device can completely inhibit the formation of such a biofilm and eliminate any detectable, viable bacteria from the inoculated pocket, as demonstrated in each of these infection models.

Conclusions: In summary, the establishment of multiple animal models of device-related infections using clinically relevant bacterial strains allows efficacy testing of a variety of antimicrobial products. Application of defined sonication and subsequent agar culture techniques provides a consistent and quantitative method to evaluate the relative amount of bacterial burden on each explanted device. In addition, a review of these studies provides insight into conditions necessary for the development of device-related infection.