JOHNS HOPKINS MEDICINE

The Pathogenesis, Diagnosis and Treatment of Orthopaedic Implant-Associated Infections

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Prosthetic joint infection (PJI) is among the most devastating complications following total hip and knee arthroplasty. In order to address different approaches to the study of the pathogenesis, diagnosis and treatment of orthopaedic implant-associated infections, several different sets of experiments were undertaken. These studies included:

- Oral-only linezolid rifampin is highly effective compared with other antibiotics in periprosthetic joint infection: a mouse model
- Preclinical evaluation of photoacoustic imaging as a novel noninvasive approach to detect an orthopaedic implant infection
- Novel preclinical model of gram negative prosthetic joint infection
- Influence of the physis in hematogenous seeding of a preclinical prosthetic joint infection
- Novel anti-staphylococcal IsaA as a fluorescence and PET imaging probe to diagnose infection

Due to space limitations, representative examples of the research projects will be summarized.

Current U.S. treatment algorithms for biofilm-associated PJI recommend two-stage revisions with intervening antibiotic therapy, of which vancomycin plus rifampin has become the new gold standard. Both of these antibiotics are widely available and relatively well-tolerated. However, this treatment algorithm requires use of PICC lines, which are both costly and cause morbidity/mortality for patients. Moreover, two-stage revisions also result in significant costs and morbidity/mortality, and efficacious nonoperative treatment would be preferable.

Newer antibiotics such as daptomycin, linezolid and ceftaroline have preliminarily shown promise in treating PJI, but they currently are second-line recommendations at best. With the recognition of powerful biofilm-penetrating agents such as rifampin, we sought to assess the efficacy of these newer agents with and without rifampin in treatment of an MRSA PJI in a non-operative fashion.

Overall, our results suggest that single agent linezolid may be a viable option at a lower dose with potentially less toxicity. Otherwise, single-agent ceftaroline, daptomycin or doxycycline are not effective therapies to treat PJI nonoperatively. Combination therapies, as shown in the vancomycin+rifampin group, may be the most effective treatments.

In another study, our aim was to create a reliable gram-negative model for PJI using *Pseudomonas aeruginosa* or *Escherichia coli* that can be tracked with BLI. Pseudomonas at all inocula (1e3, 1e4, and 1e5) produced a consistent infection based on CFU in both the tissue as well as the pin, but BLI did not correlate well at the lower inocula of 1e3. *E. coli* at inocula of 1e3 and 1e4 had no recoverable CFUs, and BLI dropped below the level of detection by day 14. We are currently working on *E. coli* at an inoculum of 1e5 and also will obtain X-ray, SEM and potentially histology for pseudomonas PJI. *E. coli* will be assessed for these elements as well if 1e5 has reliable infection at day 21. Future directions with this model could include assessing antibiotic therapies in the ability to treat gram-negative PJI nonoperatively. Based on results

from the prior antibiotic therapy project, it may be beneficial to focus on combinatorial therapies. This model could also be used to assess polymicrobial gram-negative infections, which tend to occur as opposed to single organism gram-negative infections, assuming that we can obtain and/or develop a gram-negative strain with a different bioluminescent construct than the one currently being used.

Differentiating PJI from sterile inflammation is challenging with only contemporary diagnostic techniques such as clinical imaging, blood tests and bacterial cultures. Positron emission tomography (PET) is a noninvasive imaging modality without the implant artifacts suffered by CT and MRI. By directly targeting the infecting bacteria, we demonstrated the potential for diagnosis, monitoring and assessing treatment noninvasively via immunoPET.