Case Study: Using Ultrasound and Microbubbles to Augment DAIR Treatment of Infected Total Knee Megaprosthesis

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INTRODUCTION: Periprosthetic joint infection (PJI) is a devastating complication in arthroplasty, often resulting in recurrence, prolonged antibiotic usage for mitigation, and patient morbidity. We have previously demonstrated that antibiotic activity against methicillin-sensitive *Staphylococcus aureus* (MSSA) aggregates could be increased using ultrasound-triggered microbubble destruction (UTMD) *in vitro* and in a porcine model of septic arthritis *in vivo* [1]. Here, we present an off-label use of Definity microbubbles and intraarticular antibiotics in a single patient presenting with MSSA infection of a right knee megaprosthesis.

METHODS: The patient is a 49-year-old female with a past medical history of right knee osteochondral sarcoma, for which she previously underwent proximal tibial resection and megaprosthesis arthroplasty, and several other cancers and cervical epidural abscess. Following oral suppressive therapy for the abscess, the patient presented to our emergency department with new-onset right knee pain, swelling, and fever. Aspiration of the right knee joint yielded 97,000 white blood cells/μL in synovial fluid and 95% neutrophils, raising concern for a periprosthetic joint infection (PJI) involving the tumor megaprosthesis which spans the majority of her tibia and femur. Given the location of the PJI in the setting of a tumor megaprosthesis with limited residual host bone stock, any attempt at prosthesis explantation would be associated with maximal morbidity, including the high likelihood of above-knee amputation and increased risk of mortality. Our multidisciplinary team (consisting of orthopedic surgeons and fellows, an ultrasound physicist, a biomedical engineer, microbiologist, and a radiologist) therefore developed a limb-salvage treatment strategy, consisting of two staged surgical debridement procedures with implant retention (DAIR: Debridement, Antibiotics, and Implant Retention), followed by systemic antimicrobial therapy (intravenous cefazolin) as directed by the Infectious Diseases service. We also performed an off-label Compassionate Use adjunctive UTMD in combination with direct, local antibiotic administration following the DAIR surgical procedures following approval by the IRB of our institution. The goal of this adjuvant compassionate use therapy was to potentially improve antibiotic delivery and efficacy at the prosthetic interface, thereby increasing the probability of successful limb salvage, and potentially avoiding a high-level and high-risk amputation. Our team performed three UTMD interventions over 7-10 days following each DAIR procedure, for a total of 6 UTMD interventions. Our first UTMD procedure was performed approximately 72 hours after the DAIR procedure. The joint was sterilized prior to intraarticular injection of a solution containing reconstituted Definity (1.5mL) and a combination of vancomycin (500 mg) and tobramycin (1.2g) in 15mL sterile saline mixed within one syringe equipped with an 18-gauge needle. Next, sterile ultrasound gel was added to the probe and the UTMD protocol was initiated using CEUS flash-replenishment sequences at 1.5-6.5 MHz central frequency (GE Logiq E10 scanner). The flashes operated at a mechanical index (MI) of 1.4 for 10 cycles over 4 seconds, followed by replenishment sequences at an MI of 0.2 to visualize wash-in of additional microbubbles. These cycles were repeated for approximately two hours spanning the length of the entire implant on both sides of the leg and the back of the knee.

RESULTS SECTION: Both DAIR surgeries were successful and well-tolerated. Additionally, the patient tolerated all 6 of the UTMD procedures with no serious adverse events (SAEs). During the intraarticular injection during the 6th visit, the patient exhibited a transient pain response to the injection with some flushing, sweating, and headache. These effects were transient, and resolved quickly following some water and a cool compress. Once this pain response resolved, the UTMD procedure was performed. The patient did not exhibit any pain, discomfort, or any other side effects during or after the UTMD procedures. Following both DAIR procedures, as well as the second UTMD procedure, a small amount (< 1mL) of wound fluid was aspirated and sent for culture in the clinical microbiology lab. These cultures resulted in no bacterial growth, suggesting successful mitigation of active infection. Importantly, the microbubbles were clearly visible within not only the intraarticular space but also along the shafts of the megaprosthesis, both in the thigh and the calf. This exciting finding suggests that the microbubbles and injected antibiotics are able to reach the areas of the bone-implant interface that cannot be directly debrided during the DAIR surgical procedure, providing additional prophylaxis adjunctive to the standard of care.

DISCUSSION: To date, the patient has no symptoms of infection recurrence nor signs of any implant degradation or dysfunction as a result of the DAIR and UTMD treatments. As of her latest follow up visit with her primary care physician, she is doing well and proceeding with physical therapy as part of standard of care. We recognize that our sample size is extremely limited at one patient, but we feel the results and safety profile are promising and important to the community as a whole. A larger three-site clinical trial using this UTMD adjunctive treatment will begin later this year.

SIGNIFICANCE/CLINICAL RELEVANCE: Infections in patients receiving total knee joint replacements, also known as arthroplasty, are devastating, and often result in chronic pain and long-term antibiotic use to mitigate symptoms. We aim to augment clinical attempts to treat joint infections and prevent re-infection by using ultrasound and microbubbles in the joint following revision surgery to enhance antibiotic activity. We also expect that this technique, if shown successful, can be applied to other joint sites, as well as initial arthroplasties, to help prevent chronic infections for millions of patients.

REFERENCES: 1. Zhao, N. et al. (2023) *Commun Biol*, 6(1): article ID: 425.

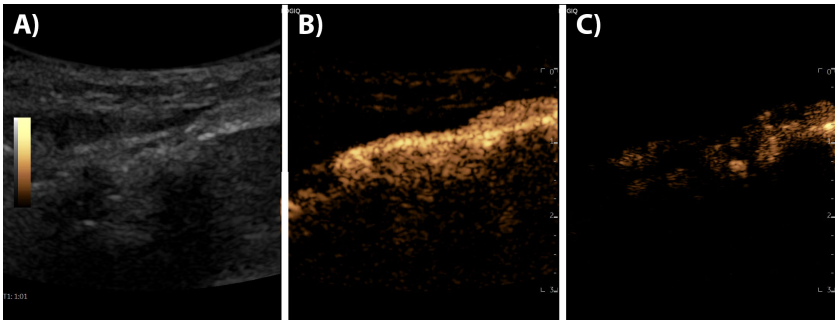

Figure 1: Ultrasound images of UTMD procedure. A) Grayscale anatomy image of knee prosthesis. B) Antibiotic+microbubble solution in intraarticular space prior to flash for UTMD. C) Intraarticular space immediately following UTMD flash showing microbubble destruction.