

EP046: A novel adjunct to DAIR for limb salvage in megaprosthesis infection: ultrasound-triggered microbubble destruction

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Case Study ➤ Can ultrasound-triggered microbubble destruction (UTMD) after DAIR increase antibiotic access to the bone-implant interface to ultimately reduce PJI recurrence?

INTRODUCTION

- Periprosthetic joint infection (PJI) of a megaprosthesis is devastating
- Debridement, antibiotics, and implant retention (DAIR) is incomplete at bone-implant interfaces
- Microbubbles are contrast agents whose ultrasound-triggered cavitation effects include shock waves, streaming, and microjets. Therapeutic uses include permeabilizing tumors for drug delivery, lysis of fibrin clots, and opening the blood brain barrier for drug access.
- In animal studies, ultrasound-triggered microbubble destruction (UTMD) augmented antibiotic action.

CLINICAL PRESENTATION

- 49 year old female:
- Previous right knee osteochondral sarcoma with proximal tibial resection and megaprosthesis arthroplasty and other cancers and cervical epidural abscess
 - On oral suppressive therapy for abscess
 - Presented to ED with new-onset right knee pain, swelling, and fever
 - Knee joint aspiration yielded 97,000 white blood cells/ μ L in synovial fluid with 95% neutrophils—PJI?
- Given the location of the PJI in the setting of a tumor megaprosthesis with limited residual host bone stock, prosthesis explantation would be associated with maximal morbidity, including the high likelihood of above-knee amputation and increased risk of mortality.*

TREATMENT STRATEGY

- Team: Orthopedic oncologist, resident, ultrasound physicist, biomedical engineer, microbiologist, and radiologist
- Limb-salvage treatment strategy:
- Two-staged surgical debridement with implant retention (DAIR: Debridement, Antibiotics, and Implant Retention), with systemic intravenous cefazolin
 - After each DAIR (**Figure 1**, first intervention at ~72 hours):
 - Over 7-10 days, 3 staged (total=6) treatments with antibiotics+UTMD
 - After the joint was sterilized, intraarticular injection of reconstituted Definity (1.5mL) microbubbles with vancomycin (500 mg) + tobramycin (1.2g) in 15mL sterile saline mixed within syringe with 18-gauge needle.
 - Sterile ultrasound gel was used and the UTMD performed with contrast-enhanced ultrasound (CEUS) flash-replenishment sequences at 4.5 MHz (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 (**Figure 2**).
 - 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.



Figure 1. Photos of post-operative ultrasound procedure. Left: Intervention #1 approximately 72 hours after first DAIR procedure. Right: Intervention #3 approximately 9 days after the first DAIR procedure.

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RESULTS

- Both DAIR surgeries were successful and well-tolerated.
- Patient tolerated the 6 UTMD procedures with no serious adverse events and did not exhibit any pain, discomfort, or any other side effects during or after the UTMD procedures.
 - At the 6th visit, the patient exhibited transient pain during the injection with some flushing, sweating, and headache. These effects resolved quickly following water and a cool compress.

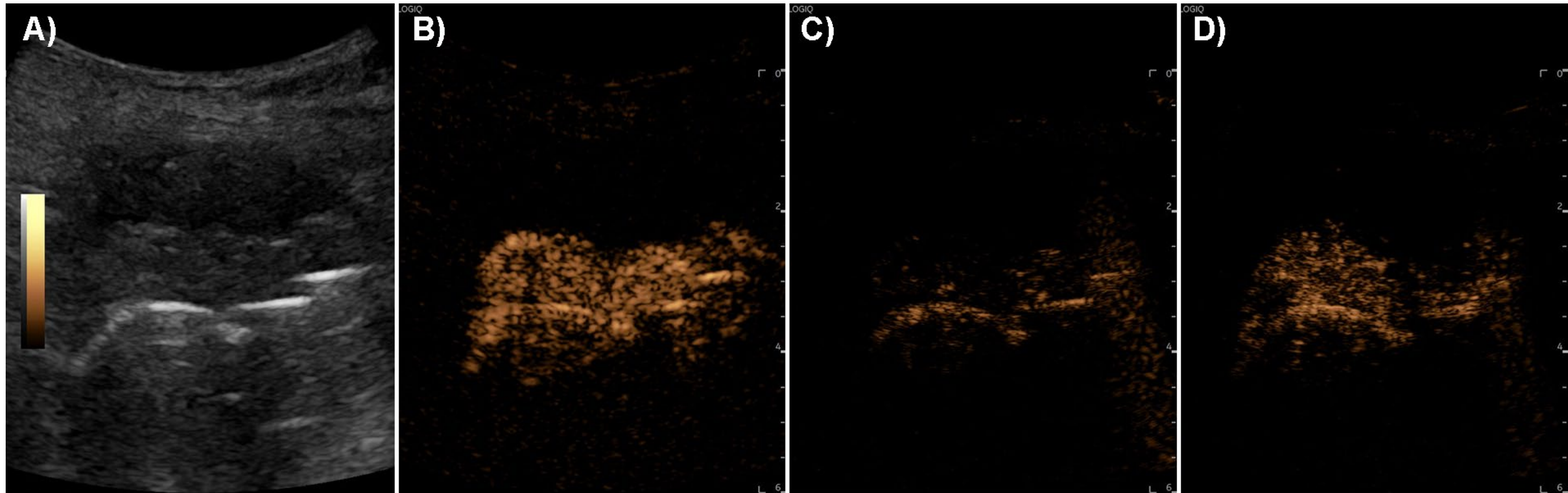


Figure 2. Representative UTMD images. A) Grayscale anatomy image of knee prosthesis and intraarticular joint space. B) Antibiotic + microbubble solution in the intraarticular space prior to UTMD flash. C) Intraarticular space immediately following UTMD flash showing localized microbubble destruction. D) Intraarticular space 45 seconds after UTMD flash showing microbubble wash-in signifying fluid movement and treatment dispersion.

- After the two DAIR procedures and at the second UTMD procedure,
- < 1 mL of wound fluid was aspirated for bacterial culture
 - The clinical microbiology lab reported no bacterial growth
- Imaging:
- Microbubbles were clearly visible within the intraarticular space
 - Microbubbles apparent along the diaphyseal bone-implant interfaces of the megaprosthesis in both the distal thigh and the distal calf (**Figure 3**).

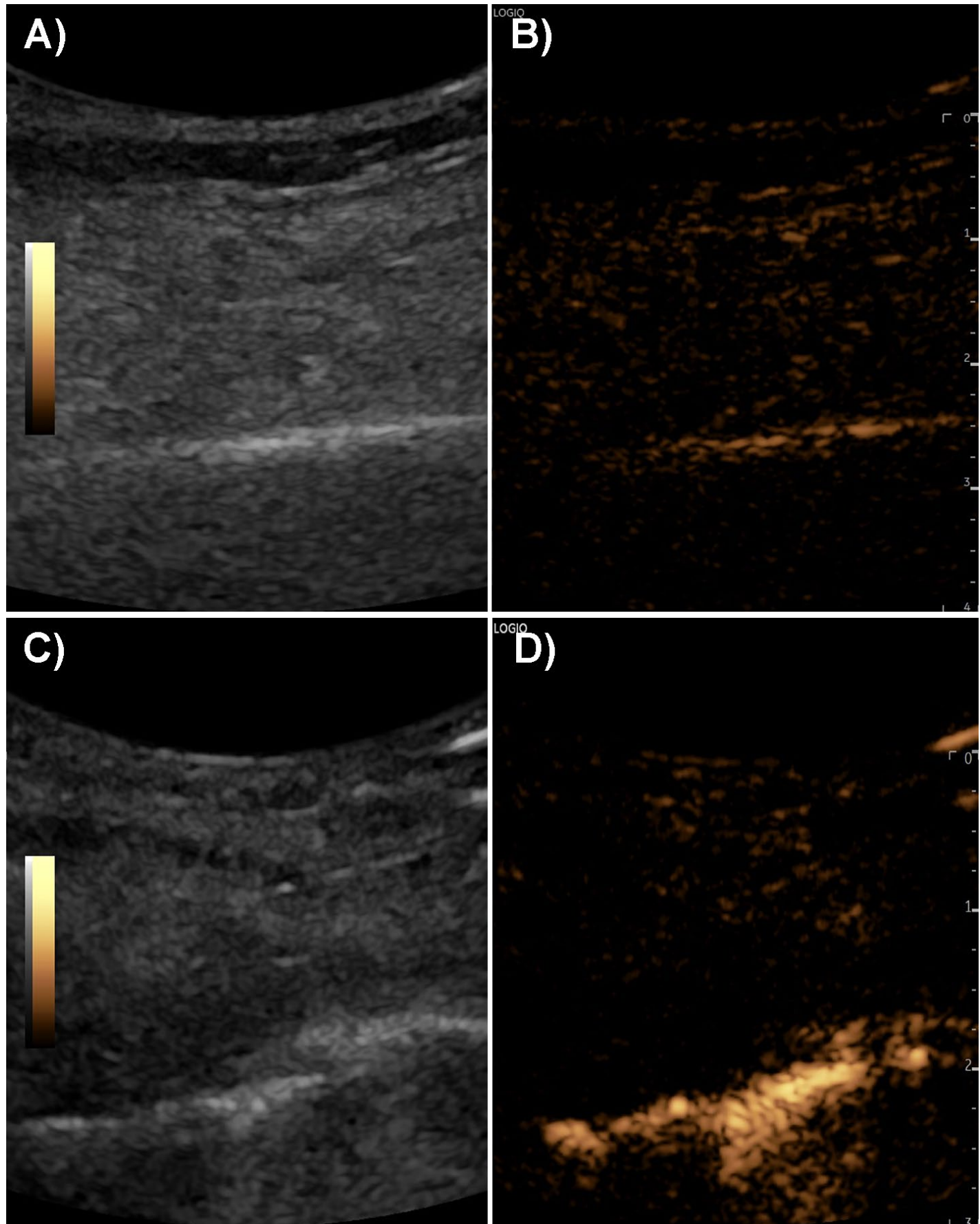


Figure 3. Representative dual grayscale/contrast-mode ultrasound imaging of antibiotic + microbubble solution visible along the (A-B) femoral (A – anatomical grayscale, B – contrast image) and (C-D) tibial (C – anatomical grayscale, D – contrast image) components of the megaprosthesis.

- Visibility of microbubbles/injected antibiotics show access to the bone-implant interface that cannot be directly debrided during the DAIR surgical procedure.
- At 6-months post-treatment, she was weight-bearing and ambulating with use of an assisted device.
- Her incision had completely healed without complications.
- To date, the patient has no symptoms of PJI recurrence nor signs of implant dysfunction.
- No symptoms of infection recurrence nor signs of any implant degradation or dysfunction as a result of the DAIR and UTMD treatments.
- At her latest follow up, she is doing well and proceeding with physical therapy as part of standard of care.

CONCLUSIONS

UTMD represents a novel, mechanistically distinct adjunctive strategy that enhances antimicrobial activity and increases access to difficult sites by leveraging the physical effects of microbubble cavitation. This case provides the first clinical demonstration of UTMD with antibiotics as an adjunct to staged DAIR in the treatment of megaprosthesis-associated PJI. We propose enhanced antibiotic action and access through adjunct UTMD treatments as a powerful, non-invasive, immediately adoptable approach for PJI treatment.