INTRODUCTION:
Although anti-resorptive agents are used to prevent osteolysis in patients with infected orthopaedic implants, this practice is anecdotal and the effects of these drugs on the bacterial load and reactive bone formation during the establishment of osteomyelitis (OM) have never been studied. Here we utilize a bioluminescent strain of Staphylococcus aureus (Xen29) and longitudinal bioluminescent imaging to quantify infection during implant-associated OM, which was confirmed by PCR. We also utilize micro-CT to evaluate anti-resorptive drug effects on osteolysis and reactive bone formation around the implant.

METHODS:
Mice were treated with placebo, gentamycin, alendronate, OPG or TNFR:Fc and then challenged with a trans-tibial pin that was contaminated with 5 million CFU of Xen29. The bioluminescence intensity (BLI) of the infected tibia was determined on day 4, 7, 11, 14, 18. The tibiae were harvested on day 18 and analyzed by micro-CT to determine the maximum osteolytic area, histology (H&E, TRAP, Gram) and real time quantitative (RTQ)-PCR to determine the number of bacterial nuc genes standardized to a beta-actin control.

RESULTS & DISCUSSION:
Placebo treated mice demonstrated a sharp increase in BLI that peaked on day 4 and then dropped down to undetectable levels by day 14 (Figure 1). Micro-CT analyses revealed that the infection cause a 10-fold increase in the size of the pin hole (Figure 2). The presence of bacteria was also confirmed by histology and RTQ-PCR. Gentamycin completely prevented the infection as assessed by all outcome measures. In contrast, alendronate and OPG treatment significantly increased BLI on days 4 and 7 post infection, but failed to affect the bacterial load at later time points, which was confirmed by RTQ-PCR. Interestingly, Aln and OPG treatment completely inhibited cortical bone loss around the pin, but did not alter the lack of reactive bone around the pin, demonstrating for the first time that osteolytic lesions caused by OM are the result of osteoclastic bone resorption of the cortical bone and inhibition of osteoblastic reactive bone formation. TNFR:Fc treatment resulted in a marked increase in BLI at all time points although its effects on bone resorption were not as potent as that observed in the alendronate and OPG groups. Furthermore, Gram staining confirmed that all of the detectable bacteria in the PBS, Aln and OPG groups were contained in necrotic bone. In contrast, TNF blockade resulted in soft tissue absesses within the bone marrow, which likely accounted for the significant increase in bacteria detected after 18 days. These results indicate that anti-resorptive therapy to prevent osteolysis around an infected orthopaedic implant may be counter indicated, as it acutely exacerbates the infection. However, selective osteoclast inhibition was not immunosuppressive and did not lead to uncontrolled bacterial growth as TNF inhibition did.