Day 14 Marks the Histological Transition from Acute to Chronic Periprosthetic Joint Infection in a Murine Arthroplasty Model

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INTRODUCTION: Periprosthetic joint infection (PJI) remains one of the most challenging complications in arthroplasty due to its heterogeneous presentation, ranging from acute, fulminant infections to chronic, biofilm-mediated disease. Accurate staging is critical because outcomes after debridement, antibiotics, and implant retention (DAIR) decline sharply from 74% within 30 days to 44% in chronic cases. Current staging relies primarily on symptom duration rather than objective histological criteria, highlighting the need for better-defined markers. We hypothesized that histological patterns in a load-bearing murine tibial implant model could define the inflammatory transition from acute to chronic PJI.

METHODS: All animals were female C57BL/6J mice (n=29). Females were chosen to minimize variability in tibial size and surgical access, and because prior murine PJI studies have used females for reproducibility. A unilateral proximal tibial implant was placed and inoculated with 3 × 10^4 CFU of Staphylococcus aureus (MSSA, Xen36; PerkinElmer, Waltham, MA). Animals were euthanized at prespecified timepoints: 48 hours (n=3), day 7 (n=6), day 10 (n=6), day 14 (n=6), day 18 (n=4), day 21 (n=2), and day 28 (n=2). Allocation favored early timepoints to maximize precision around the anticipated day-7 to day-14 transition. Radiographs and serum inflammatory markers were obtained. Limb sections were processed for H&E staining and graded (0–3) for neutrophils, macrophages/lymphocytes, edema/fibrin, and bone necrosis. Acute infection was defined a priori as neutrophils ≥2 with macrophages/lymphocytes ≤1. Chronic infection was defined as macrophages/lymphocytes ≥2 with fibrosis or necrosis ≥1. A board-certified pathologist, blinded to timepoint, scored and reviewed all slides. All animals were ambulatory and load bearing until euthanasia. All procedures were approved by the Institutional Animal Care and Use Committee. The prespecified primary endpoint was the histologic transition from acute to chronic per defined criteria.

RESULTS: At day 7, peak neutrophil infiltration and edema/fibrin deposition were observed (grade 3), with microabscess formation and early bone remodeling evident in the peri-implant region (Figure 1C). By day 14, neutrophil and edema/fibrin scores declined significantly (grades 0–1), while macrophage/lymphocyte infiltration and fibrosis increased (grades 2–3), consistent with progression toward chronic inflammation (Figure 1D). Radiographs confirmed stable intramedullary implant positioning (Figure 1A), and whole-section H&E highlighted the peri-implant inflammatory distribution (Figure 1B). Bone necrosis first appeared after day 18 and progressed thereafter. These findings demonstrate a distinct histological shift from acute neutrophil-driven inflammation at day 7 to macrophage-dominant chronic inflammation by day 14.

DISCUSSION: This murine tibial implant model demonstrates that acute PJI is characterized by neutrophil-predominant inflammation peaking at day 7, while the transition to macrophage-dominant chronic inflammation occurs by day 14, with bone necrosis evident after day 18. These histological changes mirror the progression seen in human periprosthetic membranes. Limitations include the single bacterial strain and murine-specific immune responses, which may not fully replicate human disease. Nonetheless, the defined acute-to-chronic transition window provides a histological framework for refining clinical staging and optimizing the timing of interventions such as DAIR.

SIGNIFICANCE / CLINICAL RELEVANCE: Defining objective histological markers of acute and chronic PJI improves staging beyond symptom duration alone. Recognizing the 7–14 day transition window may guide timely clinical interventions and reduce progression to chronic, treatment-resistant infection.

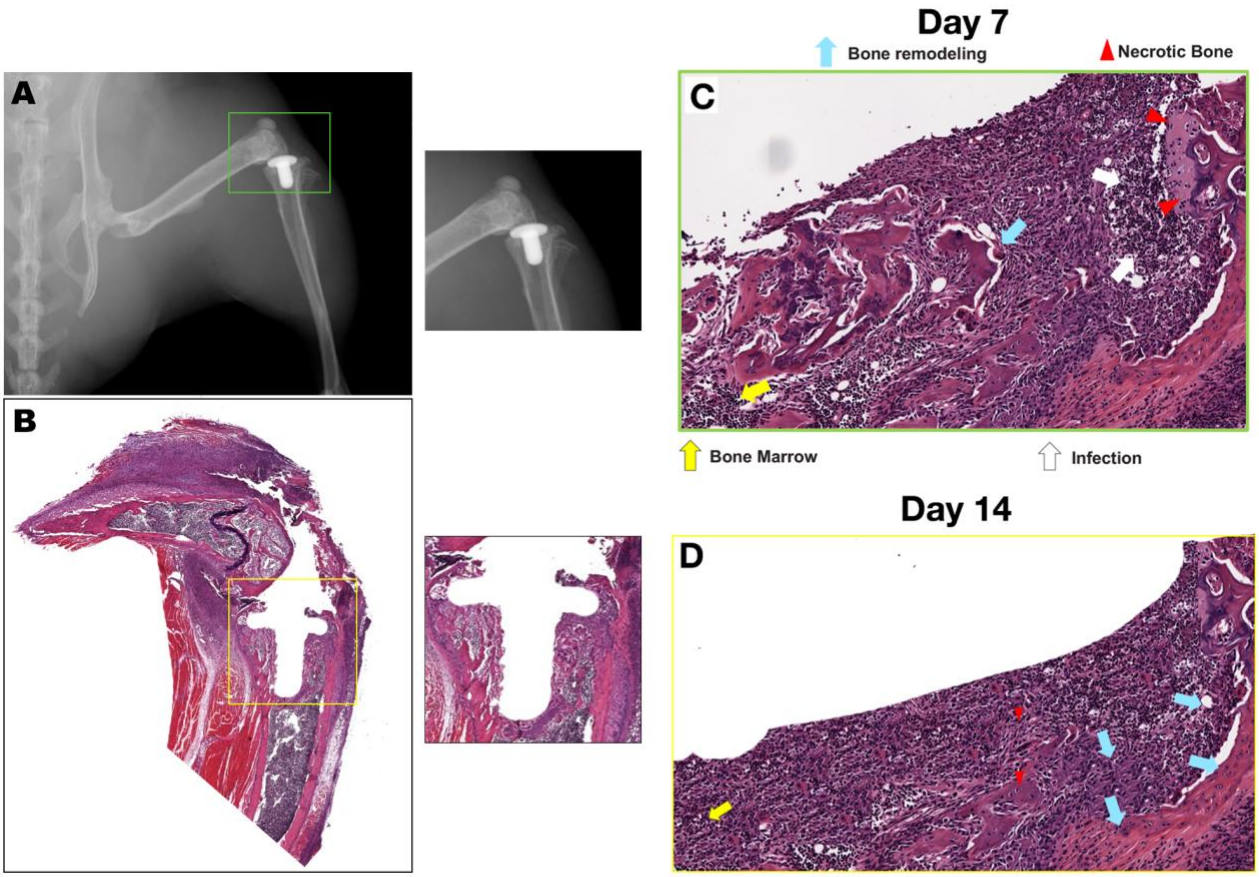

Figure 1. (A) Antero-posterior radiograph of the mouse tibia showing the intramedullary implant (green outline). **(B)** Whole section H&E of the same limb; the yellow box marks the peri-implant region of interest (ROI). **(C)** Day 7 peri-implant ROI: grade 3 neutrophil infiltrate with oedema and micro-abscesses; early bone remodelling (blue arrows), necrotic bone (orange arrowheads), infection front (white arrows) and bone marrow interface (yellow arrow). **(D)** Day 14 peri-implant ROI: neutrophils largely absent, macrophage-rich tissue and woven bone along the implant surface, consistent with progression toward the chronic phase.