**Introduction:** First generation cephalosporins provide effective prophylaxis against most skin flora but may not adequately cover low virulence organisms, including coagulase negative staphylococcus. We performed this study to assess the relative effectiveness of PJI prophylaxis using a first-generation cephalosporin (Ancef) alone, ancef + vancomycin (A-V) or ancef + gentamicin (A-G), and the associated risks of renal impairment.

**Methods:** After obtaining IRB approval, we retrospectively reviewed 3,337 consecutive primary and revision lower extremity total joint arthroplasties, including 1,428 patients receiving Ancef alone (A), 1,178 patients receiving cefazolin and a single dose of vancomycin (A-V), and 731 patients receiving cefazolin and a single dose of gentamicin (A-G). A chart review was performed to determine patient demographic characteristics, physiological response to surgery, and incidence of subsequent septic or aseptic surgical procedures. Statistical assessment was accomplished using a paired student’s T-test or Fisher’s Exact Test, with a p-value < 0.05 accepted as significant.

**Results:** Dual-agent A-V prophylaxis had substantially lower infection rates during the first 2 years after primary TJA compared with patients receiving either A or A-G prophylaxis (1.6% vs 2.9%, p=0.04) and after revision THA also (1.1% vs 12.5%, p=0.04). Patients who received Ancef alone and sustained a periprosthetic infection were more likely to have polymicrobial infections (25% vs 10%, p=0.05) or MRSA infection (13.8% vs 2.8%, p=0.04) than patients who received either dual-antibiotic PJI prophylaxis. There was a trend towards a proportion of patients with uncorrected creatinine elevation > 1.5 mg/dl (0.4% vs 0.07%, p=0.06), but no patients in the A-V group required hemodialysis.

**Conclusion:** While first generation cephalosporins lower PJI infection rates, infections with low virulence organisms may still occur. In our institution, the addition of a single dose of Vancomycin effectively reduced PJI infection rates in primary TJA and revision THA with a low risk of renal impairment.