



**CASE STUDY**

**Acute Kidney Injury Following Antibiotic Spacer Placement for Two-Stage  
Arthroplasty**  
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**ABSTRACT**

Chronic infection of the joint following total knee arthroplasty is often treated with a two-stage revision process. This involves explantation of the infected hardware and implantation of an antibiotic impregnated cement spacer. Recipes for addition of antibiotics to the cement are variable and can be surgeon specific. Systemic toxicity from the antibiotics can occur but has historically been documented as a rare occurrence. A 71 year old female with a history of total knee replacement developed a case of septic arthritis in the artificial joint following a urinary tract infection. The patient was treated with the first part of two- stage revision including explantation of infected hardware, placement of a tobramycin impregnated spacer, and planned placement of a permanent prosthesis. Following discharge, the patient presented back to the emergency room with acute kidney injury with a significantly elevated tobramycin level (13.4 mcg/ml). The patient required hemodialysis and explantation of the antibiotic spacer before achieving full recovery of baseline renal function. A two-stage revision with implantation of antibiotic laden cement (ALC) is the standard of care for late chronic infection of knee prosthesis. Antibiotic composition of the spacer is variable with no true standard recipe. ALC utilizes much higher doses of antibiotics within the cement than are given intravenously. Traditionally, ALC spacers have been shown to be safe and effective without a high incidence of systemic toxicity. Despite this notion, systemic toxicity can occur. When high dose aminoglycoside therapy is used, routine renal function monitoring may be considered.

**KEYWORDS**

Antibiotic Laden Spacer, Tobramycin, Toxicity

**INTRODUCTION**

Total knee arthroplasty is one of the most common procedures in the United States with over 600,000 cases performed annually.<sup>1</sup> Although occurring somewhat infrequently (0.5-3% of cases), infection carries a high risk for morbidity.<sup>2</sup> When post-operative infection does occur, standard of care involves a two-stage revision with placement of an antibiotic laden cement (ALC) spacer.<sup>2</sup>

The spacer serves two distinct purposes: first, to preserve joint space and mobility and secondly, to deliver high local concentrations of antibiotics without systemic toxicity.<sup>3</sup> Despite the intent to minimize systemic absorption and therefore adverse effects, patients can experience systemic toxicity. Given that vancomycin and aminoglycosides are the most commonly used antibiotics for these procedures, it is not surprising that acute kidney injury (AKI) can occur if systemically absorbed.<sup>3</sup>

While the orthopedic surgeons carrying out these revisions may be well versed in amounts

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and types of antibiotics mixed into ALC and potential resulting toxicity, this is not likely a topic encountered by many practicing pharmacists. Furthermore, a 2013 review identified 10 observational studies and 5 case reports addressing patients with AKI following two stage revisions.<sup>3</sup> A review of the article and corresponding references revealed that the vast majority of studies and cases are published in orthopedic specific journals, without a pharmacist specific target audience. As such, pharmacists should be educated about the process and specific systemic complications which may arise following placement of antibiotic spacers.

This is a case report of systemic tobramycin absorption with acute kidney injury in a patient with two-stage total knee arthroplasty revision following prosthesis infection.

## CASE

A 71 year old Caucasian female with a history of right total knee replacement in 2010 developed a urinary tract infection which grew *Escherichia coli* in July 2013 and was treated with oral antibiotics. After that event, the patient developed recurrent pain in her right knee. In September 2013, the patient underwent an outpatient aspiration of the joint which revealed 40,000 white blood cells with 93% neutrophils and 80,000 red blood cells. Subsequent aspiration and surgical tissue cultures produced an E-coli susceptible to all tested agents except ampicillin/sulbactam and aztreonam.

The patient then elected to undergo a right knee two-stage revision arthroplasty with “placement of a tobramycin and gentamicin loaded cement” containing 7.2 g of tobramycin as well as 1g of gentamicin already present in the cobalt cement. A total of three batches of cement were used. Antibiotic beads were also placed up and down the femoral and tibial canals. The composition of the antibiotic beads was not detailed in the operative report. The patient’s pre-operative renal labs included: sodium 136 mmol/l, potassium 4.6 mmol/l, chloride 102 mmol/l, carbon dioxide 25 mmol/l, blood urea nitrogen (BUN) = 26 mg/dl, and serum creatinine was

1.2 mg/dl. The patient was noted to have had past serum creatinines ranging from 1.1-1.5 mg/dl. The patient had a past medical history of diabetes mellitus type 2, hypertension, and chronic liver disease. Following standard post-operative care including infectious disease consultation with recommendations for a 6 week course of ceftriaxone 2 grams intravenously daily and levofloxacin 500mg po daily, the patient was discharged to a rehabilitation facility on post-operative day (POD) 3. Potential nephrotoxic discharge medications included: furosemide 20mg po daily and chlorthalidone 12.5mg po daily.

On POD 15, the patient presented to the emergency room with intermittent nausea and generalized weakness. Lab work in the emergency department revealed the following: sodium 130 mmol/l, potassium 2.7 mmol/l, BUN 60 mg/dl, and serum creatinine 5.8 mg/dl. Initial diagnosis per nephrology consultation included acute kidney injury with pre-renal azotemia secondary to lack of oral intake with nausea and also diuretic use versus acute interstitial nephritis from the beta lactam antibiotics.

With supportive measures providing little to no improvement, a tobramycin random level was ordered on POD 17 with a result of 13.4 mcg/ml. A temporary hemodialysis catheter was placed and the patient started hemodialysis the same day. The tobramycin random level on POD 18 was reported as 3.8 mcg/ml but increased to 6.8 mcg/ml on POD 19. A decision was made to explant the antibiotic cement spacer and this was carried out on POD 21 with both antibiotic cement and bead removal and placement of antibiotic free cobalt cement.

The patient continued hemodialysis until dialysis catheter was removed 7 days after ALC explant. Patient was deemed ready for discharge on day 10 after explantation. She was discharged to a rehabilitation facility with the last tobramycin random level = 0.8 mcg/ml and a discharge creatinine of 2.3 mg/dl.

The patient was seen in the emergency department of Saint Joseph hospital

approximately one month after explantation of ALC for tachycardia and hypertension with a serum creatinine of 1.0 mg/dl and BUN of 21 mg/dl. Application of the Naranjo algorithm for adverse reaction probability would classify this specific case as a definite adverse drug reaction.<sup>4</sup>

## DISCUSSION

Total knee arthroplasty infections can occur immediately post operatively or even much later. Site infections are commonly classified into four categories: acute postoperative (within 4 weeks of operation), late chronic ( $\geq 4$  weeks after the operation), acute hematogenous (acute onset at the site of a previously well-functioning joint replacement), or positive intraoperative culture ( $\geq 2$  positive intraoperative cultures).<sup>2</sup> Each category of infection requires individualized treatment and delivery of antibiotics. For late chronic infection after total knee arthroplasty, two-stage revision surgery is standard of care.<sup>2</sup>

Two-stage revision involves removing prosthetic implants, treatment of infection, and later re-implantation of new prosthetic hardware. After removal of the prosthesis, antibiotic-impregnated spacers are now routinely placed to treat local infection. The spacers accomplish several goals. The obvious benefit is local delivery of antibiotic to site of infection at high local concentration without theoretical systemic antibiotic exposure. Secondly, the spacer provides joint stability and preserves patient mobility. Third, the spacer placement facilitates re-implantation surgery.<sup>2</sup>

In terms of preparation, spacers may be commercially produced or custom made in the operating room. Often, the custom made spacers consist of polymethylmethacrylate cement with antibiotics embedded in the cement according to culture results and likely pathogens.<sup>2</sup> Custom made spacers are actually the standard of care for delivery of site specific antibiotics to established infections. Commercial spacers contain lower amounts of antibiotics (e.g., Simplex P, a commercial spacer contains 1g of

tobramycin) which are suitable only for prophylaxis period.<sup>2</sup>

Many different recipes for bone cement have been used without a true "standard". It is important to recognize that doses of antibiotics that are mixed into bone cement are much higher than traditional intravenous formulations of the same antibiotics. A recent review article listed the various amounts of vancomycin, gentamicin, and tobramycin used in cement spacers for two stage arthroplasty in a review of the literature. Vancomycin utilized per 40 g batch of cement ranged from zero to 8g. Gentamicin doses range from zero to 2g per 40 g of cement, while tobramycin ranged from zero to 7.2g. It should be noted that there were several instances where gentamicin, tobramycin, or vancomycin were already present in the base cement from the manufacturer and additional amounts of vancomycin, gentamicin, or tobramycin were added.<sup>3</sup> Additionally, some formulations included both gentamicin and tobramycin in the same cement mixture. One study described 9 cases where vancomycin and tobramycin were added to commercial cement already containing 0.5g of gentamicin.<sup>5</sup>

Elution of antibiotics is variable and is effected by the cement composition. Factors affecting antibiotic elution include: the choice of antibiotic, presence and amounts of multiple antibiotics, surface area of the spacer and the porosity of the cement.<sup>2</sup> For example, the addition of tobramycin and vancomycin together in cement increases the elution rates of both. Conversely, vancomycin should not be used as a lone antibiotic in bone cement because effective rates of vancomycin elution are not maintained at the site of infection over time.<sup>2</sup>

The elution rate of antibiotics from cement into the joint also changes over time. A three- phase elution model has been proposed: exponential phase during the first 24 hours, declining phase, and a low constant phase. By this model, antibiotic levels would be highest immediately post insertion and decline thereafter.<sup>6,7</sup>

When formulating ALC, not all antibiotics are suitable for mixture. The antibiotic must be

thermostable as polymerization of the cement is exothermic and can affect the stability of the antimicrobial. The agent must also be water soluble for delivery into local joint environment.<sup>8</sup> Additionally, empiric therapy versus pathogen specific therapy alters antimicrobial selection, just as it would with systemic antibiotics. As noted previously, vancomycin and aminoglycosides are common additives to cement. Furthermore, linezolid, daptomycin, some cephalosporins, and select quinolones have been added to antibiotic cement as well with varying results.<sup>8</sup>

With any therapy, risk versus benefit must be weighed. Compared to systemic antibiotic therapy, complications specific to ALC are rare. As recently as 2007, the following statement was published, “there are no clinical reports of systemic toxicity with tobramycin, gentamicin, or vancomycin in antibiotic laden cement.”<sup>6</sup> Another group concluded that ALC with average doses of 10.5g of vancomycin and 12.5g of gentamicin were clinically safe with no systemic side effects.<sup>9</sup> Contrary to these statements, there are examples in literature demonstrating systemic toxicity associated with ALC. A retrospective study assessed acute kidney injury with ALC spacers for total knee arthroplasty procedures. It described a 17 % incidence of AKI with a significant association with tobramycin doses >4.8g in the spacers.<sup>10</sup> A recent review summary examined the incidence of acute kidney injury with ALC. The summary documented 10 observational studies with an incidence of AKI ranging from 2% to 17 % all with varying definitions of AKI. The overall rate of AKI across the studies was 4.8%.<sup>3</sup>

## CONCLUSION

A two-stage revision with implantation of ALC is the standard of care for late chronic knee prosthesis infections. Antibiotic composition of the spacer is variable with no true standard recipe. ALC utilizes much higher doses of antibiotics with the cement than are given intravenously. Traditionally, ALC spacers have been shown to be safe and effective with low rates of systemic toxicity. When high dose

aminoglycoside therapy is used, routine renal function monitoring may be considered.

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