Acute kidney injury after hip or knee replacement: Can we lower the risk?

ABSTRACT

Patients who undergo hip or knee replacement (total joint arthroplasty) face a risk of acute kidney injury that may be higher than previously thought and that increases steeply if they undergo surgical revision to treat prosthetic joint infection. This article assesses the incidence of and risk factors for acute kidney injury after primary total joint arthroplasty or placement of an antibiotic-loaded cement spacer to treat infection, and offers suggestions on how to reduce the risk.

In primary total joint arthroplasty, significant risk factors include older age, higher body mass index, chronic kidney disease, comorbidity, anemia, perioperative transfusion, aminoglycoside prophylaxis and treatment, preoperative heart murmur, and renin-angiotensin-aldosterone system blockade.

Acute kidney injury may arise from infection, systemic administration of nephrotoxic antibiotics, and elution of antibiotics from antibiotic-loaded cement.

No randomized controlled trial aimed at reducing acute kidney injury in these settings has been published; however, suggestions for practice modification are made based on the available data.

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TOTAL HIP OR KNEE REPLACEMENT (also called total joint arthroplasty) is highly successful at relieving pain and restoring function, but at the risk of acute kidney injury, which is a sudden loss of renal function. Various factors have been associated with this risk, some of which are potentially modifiable, notably, the use of nephrotoxic antibiotics and other drugs.

This review examines the incidence of acute kidney injury using current criteria in total joint arthroplasty of the hip or knee in general, and in the setting of revision surgery for prosthetic joint infection in particular, in which the risk is higher. We identify risk factors for acute kidney injury and propose ways to lower the risk.

MILLIONS OF PROCEDURES ANNUALLY

Total replacement of the hip¹,² or knee³ is being done more and more. Kurtz et al⁴ estimate that by the year 2030, we will see approximately 3.5 million primary total knee and 500,000 primary total hip replacements every year. In addition, revision total knee procedures are expected to exceed 250,000 per year, and revision total hip procedures are expected to exceed 90,000 per year.⁵

Chronic infection may complicate up to 2% of these procedures and is associated with significant morbidity, death, and financial costs. Currently, it may be the reason for 25% of total joint arthroplasty revisions,⁵ but by the year 2030, it is projected to account for 66% of revision total knee arthroplasties and 48% of revision total hip arthroplasties.⁵
## Table 1

### Studies reporting the incidence of acute kidney injury using current diagnostic criteria

| Study      | No. of patients | Joints involved       | Definition of AKI | Incidence of AKI | Risk factors for AKI                                                                 | Comments                                                                 |
|------------|-----------------|-----------------------|-------------------|------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Jafari7    | 17,938          | Hip, knee             | "I" or "F" of RIFLE criteria | 0.55%            | BMI, chronic kidney disease, hypertension, COPD, heart failure, heart disease, liver disease | Neglected the most common "R" criteria                                   |
| Jamsa8     | 20,575          | Hip, knee             | "I" or "F" of RIFLE criteria | 0.28%            | Preoperative estimated glomerular filtration rate, ASA score, BMI                   | Only 5,609 had postoperative serum creatinine measured                    |
| Sehgal9    | 659             | Knee                  | AKIN               | 21.9%            | RASB, diabetes                                                                      | Not independent risk factors                                             |
| Weingarten10 | 7,463          | Hip, knee, shoulder    | AKIN               | 2.2%             | BMI, diabetes, PAD, perioperative transfusion, number of antihypertensive medications | 93% of AKI cases were only stage 1                                      |
| Kimmel11   | 425             | Hip, knee             | RIFLE              | 14.8%            | Age, BMI, chronic kidney disease, RASB                                              |                                                                           |
| Warth12    | 1,038           | Hip, knee             | AKIN               | 5.7%             | Age, BMI, diabetes, smoking                                                         | AKI in 4.8% of 903 with serum creatinine < 1.2 mg/dL vs 11% if ≥ 1.2     |
| Perregaard13 | 3,410          | Hip                   | KDIGO              | 2.2%             | Chronic kidney disease                                                              | AKI in 7% of 374 patients; 11% with chronic kidney disease               |
| Hassan14   | 599             | Hip                   | RIFLE              | 13.8%            | Age, hypertension, general anesthesia, dicloxicillin, low baseline blood pressure    | 1.7% became permanent dialysis patients                                  |
| Nowicka15  | 337             | Hip, knee             | AKIN               | 6.2%             | Chronic kidney disease                                                              | AKI in 16.7% with chronic kidney disease vs 4.5% without                 |
| Kim16      | 1,309           | Knee                  | KDIGO              | 4.4%             | Age, diabetes, beta-blockers, diuretics, low albumin                                 | Highlights risk of low postoperative albumin                            |
| Choi17     | 2,467           | Hip                   | AKIN               | 4.82%            | Postoperative hemoglobin < 10 g/dL                                                   | Highlights risk of anemia                                                |
| Nielson18  | 798             | Hip, knee, spinal fusion | KDIGO          | 4.26%            | RASB, BMI, intraoperative hypertension                                               | Highlights risk of RASB                                                  |
| Courtney19 | 1,828           | Hip, knee             | AKIN               | 11.3%            | Vancomycin, ASA score, reduced glomerular filtration rate                           | AKI in 13% if vancomycin given                                           |
| Dubrovskaya20 | 4,177        | Hip, knee, spine (1,502) | RIFLE            | 2.8% (hip and knee) | Diabetes, knee or hip surgery (vs spine)                                             | Not associated with prophylactic gentamicin                               |
| Bell21     | 7,666           | Hip, knee             | KDIGO              | 7.14%            | Gentamicin/flucloxacillin vs cefuroxime prophylaxis                                 | Highlights risk of gentamicin/flucloxacillin                             |
| Ross22     | 273             | Hip, knee             | RIFLE              | 4%               | Gentamicin/flucloxacillin vs cefuroxime prophylaxis                                 | Highlights risk of gentamicin/flucloxacillin                             |
| Bailey23    | 238             | Hip, knee             | RIFLE              | 5.7%             | Gentamicin/flucloxacillin vs cefuroxime prophylaxis                                 | Highlights risk of gentamicin/flucloxacillin                             |
| Challagundla24 | 198           | Hip, knee             | RIFLE              | 23.7%            | Male sex, RASB, high-dose gentamicin/flucloxacillin vs cefuroxime prophylaxis       | Highlights risk of gentamicin/flucloxacillin; AKI in 52% of 52 receiving high-dose gentamicin/flucloxacillin |
| Johansson25 | 136             | Hip                   | KDIGO              | 20%              | Gentamicin/didoxacillin vs didoxacillin                                              | Highlights risk of gentamicin                                            |
| Ferguson26  | 413             | Hip, knee             | RIFLE              | 8%               | Age, volume of postoperative fluid                                                   | RASB and gentamicin not significant                                      |
| Bjerregaard27 | 1,213        | Hip, knee             | KDIGO              | 3.5%             | Chronic kidney disease, postoperative hypotension                                    | Only considered the 1,213 patients with prolonged length of stay or 30-day readmission |
| Friedman28  | 345             | Hip, knee             | KDIGO              | 6.3%             | Preoperative murmurs, age                                                           | Odds ratio 7.73 (P < .001) for AKI if preoperative murmur               |

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; KDIGO = Kidney Disease Improving Global Outcomes; PAD = peripheral artery disease; RASB = renin-angiotensin system blockade (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker); RIFLE = risk, injury, failure, loss, end-stage kidney disease; RASB = renin-angiotensin system blockade.
We searched Ovid MEDLINE for articles on acute kidney injury and either arthroplasty or antibiotic-loaded cement spacers. We found 22 studies, with a total of 72,850 patients, that assessed the incidence of acute kidney injury after primary or revision total joint arthroplasty of the hip or knee, or both, using current criteria7–28 (Table 1), and 3 additional studies that used discharge diagnosis coding.29–31

Study designs, findings varied widely
The incidence of acute kidney injury varied markedly among the studies of primary total joint arthroplasty or revision for aseptic reasons. Numerous factors explain this heterogeneity.

### TABLE 2
Current criteria for diagnosing and staging acute kidney injury

| Criteria | Stage | Creatinine-based criteria | Urine output-based criteria |
|----------|-------|---------------------------|-----------------------------|
| RIFLE criteria | R     | Rise of serum creatinine of ≥ 50% within 7 days or decrease in GFR of 25% | < 0.5 mL/kg/hour for 6 consecutive hours |
|           | I     | Rise of serum creatinine of > 100% or GFR decrease by 50% | < 0.5 mL/kg/hour for 12 consecutive hours |
|           | F     | Rise of serum creatinine of > 200% or GFR decrease by 75% or renal replacement therapy | < 0.3 mL/kg/hour for 24 hours or anuria for 12 hours |
|           | L     | Complete loss of function for more than 4 weeks | |
|           | E     | Complete loss of renal function > 3 months | |
| AKIN criteria | 1      | Rise of serum creatinine of ≥ 50% or increase of ≥ 0.3 mg/dL in < 48 hours | < 0.5 mL/kg/hour for 6 consecutive hours |
|           | 2      | Rise of serum creatinine of > 100% or renal replacement therapy | < 0.5 mL/kg/hour for 12 consecutive hours |
|           | 3      | Rise of serum creatinine of > 200% or renal replacement therapy | < 0.3 mL/kg/hour for 24 hours or anuria for 12 hours |
| KDIGO criteria | 1      | 1.5–1.9 × baseline within 7 days or 0.3 mg/dL increase within 48 hours | < 0.5 mL/kg/hour for 6–12 hours |
|           | 2      | 2.0–2.9 × baseline | < 0.5 mL/kg/hour for ≥ 12 hours |
|           | 3      | 3 × baseline or increase to ≥ 400 μmol/L or renal replacement therapy | < 0.3 mL/kg/hour for ≥ 24 hours or anuria for ≥ 12 hours |

*Satisfaction of either creatinine-based criteria or urine output-based criteria is sufficient for diagnosis and staging. Both are not required.

AKIN = Acute Kidney Injury Network33; GFR = glomerular filtration rate; KDIGO = Kidney Disease Improving Global Outcomes34; RIFLE = risk, injury, failure, loss, end-stage renal disease32
Discharge diagnosis may miss many cases
Several studies based the diagnosis of acute kidney injury on International Classification of Diseases, Ninth Revision (ICD-9) coding from hospital discharge summaries.

Nadkarni et al,29 in the largest study published to date, used the nationwide inpatient sample database of more than 7 million total joint arthroplasties and found an incidence of acute kidney injury based on ICD-9 coding of 1.3% over the years 2002 to 2012, although this increased to 1.8% to 1.9% from 2010 to 2012.

Lopez-de-Andres et al,30 in a similar study using the Spanish national hospital discharge database, evaluated 20,188 patients who underwent revision total hip or knee arthroplasty and found an overall incidence of acute kidney injury of 0.94%, also using ICD-9 coding.

Gharaibeh et al31 used similar methods to diagnose acute kidney injury in a single-center study of 8,949 patients and found an incidence of 1.1%.

Although these 3 studies suggest that the incidence of acute kidney injury is relatively low, Grams et al35 found the sensitivity of ICD-9 coding from hospital records for the diagnosis of acute kidney injury to be only 11.7% compared with KDIGO serum creatinine and urine output criteria. This suggests that the true incidence in these studies may be many times higher, possibly near 10%.

Do all stages of kidney injury count?
Jafari et al,7 in a large series from a single medical center, used only the “I” (injury) and “F” (failure) levels of the RIFLE criteria (corresponding to stages 2 and 3 of the KDIGO criteria) and found an incidence of 0.55% in more than 17,000 total joint arthroplasties.

Jamsa et al8 used the same criteria for acute kidney injury (only “I” and “F”) and found 58 cases in 5,609 patients in whom postoperative serum creatinine was measured, for an incidence of 1%; the remaining 14,966 patients in their cohort did not have serum creatinine measured, and it was assumed they did not have acute kidney injury. Neither of these studies included the most common “R” (risk) stage of acute kidney injury.

Parr et al36 recently studied a nationwide sample of 657,840 hospitalized veterans and found that of 90,614 who developed acute kidney injury based on KDIGO creatinine criteria, 84% reached only stage R. This suggests that if all stages were considered, the true incidence of acute kidney injury would have been higher—possibly 4% in the Jafari series and possibly 7% in the Jamsa series.

Smaller studies had higher rates
Smaller, single-center series reported much higher incidences of acute kidney injury.

Kimmel et al11 found an incidence of 14.8% in 425 total joint arthroplasties using RIFLE creatinine criteria.

Johansson et al15 found an incidence of 19.9% in 136 total joint arthroplasties using KDIGO creatinine criteria.

Sehgal et al9 found an incidence of 21.9% in 659 total joint arthroplasties using AKIN creatinine criteria.

Challagundla et al24 found an incidence of 23.7% in 198 procedures using RIFLE creatinine criteria.

Weingarten et al,10 in a single-center series of 7,463 total joint arthroplasties, found an incidence of acute kidney injury of only 2.2% using AKIN criteria, although 12% of the patients with acute kidney injury did not return to their baseline serum creatinine levels by 3 months.

Our estimate: Nearly 10%
In total, in the 20 studies in Table 1 that included all stages of acute kidney injury, there were 1,909 cases of acute kidney injury in 34,337 patients, for an incidence of 5.6%. Considering that all studies but one were retrospective and none considered urine output criteria for acute kidney injury, we believe that using current KDIGO criteria, the true incidence of acute kidney injury complicating primary lower-extremity total joint arthroplasties is really closer to 10%.

Risk factors for acute kidney injury
Various factors have been associated with development of acute kidney injury by multivariate analysis in these studies. Some are modifiable, while others are not, at least in the short term.

Nonmodifiable risk factors
Older age is often significant in studies assessing primary total joint arthroplasty or revision
total joint arthroplasty not specifically for infection.\textsuperscript{11,12,16,17,26,28}

Obesity is also a major factor in the development of acute kidney injury,\textsuperscript{7,10–12,17,18} and, along with age, is a major factor contributing to the need for joint replacement in the first place.

Male sex may increase risk.\textsuperscript{29}

Diabetes mellitus was identified as a risk factor in several studies,\textsuperscript{10,12,17,20} and hypertension in a few.\textsuperscript{7,10,24}

Other comorbidities and factors such as cardiovascular disease,\textsuperscript{7,10} liver disease,\textsuperscript{7} pulmonary disease,\textsuperscript{7} high American Society of Anesthesiology score,\textsuperscript{8,19} and benign heart murmurs preoperatively by routine physical examination have also been linked to acute kidney injury after joint arthroplasty.\textsuperscript{28}

Chronic kidney disease as a risk factor
Chronic kidney disease at baseline was associated with acute kidney injury in several of these series.\textsuperscript{7,11–13,15,19,29}

Warth et al\textsuperscript{12} studied 1,038 patients and found an incidence of acute kidney injury of 11% in the 135 with chronic kidney disease (defined as serum creatinine > 1.2 mg/dL) and who received acetaminophen or narcotics for pain control, compared with 4.8% in the remaining 903 patients without chronic kidney disease, who received ketorolac or celecoxib.

Perregaard et al\textsuperscript{13} studied 3,410 patients who underwent total hip arthroplasty and found an incidence of acute kidney injury (per KDIGO creatinine criteria) of 2.2% overall, but 7% in the 134 patients with chronic kidney disease based on KDIGO creatinine criteria.

Nowicka et al\textsuperscript{15} found an incidence of acute kidney injury of 16.7% in the 48 patients with chronic kidney disease (defined as a glomerular filtration rate estimated by the Cockroft-Gault formula of less than 60 mL/min/1.73 m\textsuperscript{2}), compared with 4.5% in the remaining 289.

Modifiable risk factors
Modifiable risk factors that should be considered in high-risk cases include anemia, perioperative blood transfusion, perioperative use of renin-angiotensin-aldosterone system inhibitors such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), particular antibiotics used for prophylaxis, and nonsteroidal anti-inflammatory drugs used postoperatively.

Anemia and blood transfusion
Preoperative anemia has been associated with postoperative acute kidney injury in various surgical settings such as cardiac surgery.\textsuperscript{17,28} Perioperative red blood cell transfusions have also been associated with acute kidney injury in cardiac surgery; similar results may apply to total joint arthroplasty.

Choi et al,\textsuperscript{17} in 2,467 patients undergoing hip replacement, found a significant risk for acute kidney injury if postoperative hemoglobin was consistently below 10 g/dL compared with consistently above this level, with an inverse probability-of-treatment weighted odds ratio of 1.817 ($P = .011$).

Others have found a significant association of perioperative blood transfusion with acute kidney injury in total joint arthroplasty.\textsuperscript{10,29}

Nadkarni et al,\textsuperscript{29} for example, used the nationwide inpatient sample database and found by multivariate analysis that perioperative blood transfusion was strongly associated with acute kidney injury, with an adjusted odds ratio of 2.28 (95% confidence interval [CI] 2.15–2.42, $P < .0001$).

Comment. A higher incidence of acute kidney injury may represent confounding by indication bias, as sicker patients or complicated surgeries may require transfusion, and this risk may not be completely accounted for by multivariate analysis. It is also possible, however, that transfusions per se may contribute to acute kidney injury. Possible direct or indirect mechanisms mediating acute kidney injury include hemolytic reactions, circulatory overload, acute lung injury, and immunomodulatory effects.\textsuperscript{39}

Preoperative transfusion in anemic patients undergoing cardiac surgery may also reduce the incidence of postoperative acute kidney injury both by correcting the anemia and by limiting the need for perioperative transfusions.\textsuperscript{40} It remains to be determined whether elective perioperative transfusion to correct anemia would reduce postoperative development of acute kidney injury in total joint arthroplasty. As an aside, perioperative transfusion has also been linked to development of periprosthetic joint infection.\textsuperscript{31}
Renin-angiotensin-aldosterone system inhibitors

Several studies found perioperative use of renin-angiotensin-aldosterone system inhibitors to be a risk factor for acute kidney injury.

Kimmel et al\textsuperscript{11} reported adjusted odds ratios of 2.70 (95% CI 1.12–6.48) for ACE inhibitor use and 2.64 (95% CI 1.18–5.93) for ARB use in a study of 425 primary total joint arthroplasties.

Challagundla et al\textsuperscript{24} found an odds ratio of 3.07 (95% CI 1.40–6.74) with ACE inhibitor or ARB use by multivariate analysis in 198 total joint arthroplasties.

Nielson et al\textsuperscript{18} studied 798 patients who underwent total joint arthroplasty and found that preoperative use of renin-angiotensin system inhibitors was associated with a significantly higher rate of postoperative acute kidney injury (8.3% vs 1.7% without inhibition), which was statistically significant by multivariate analysis (odds ratio 2.6, 95% CI 1.04–6.51).

We recommend holding renin-angiotensin-aldosterone system inhibitors 7 days before surgery through the postoperative period in high-risk cases.

Aminoglycoside use as a risk factor

Prophylactic administration of systemic antibiotics is the standard of care. In a systematic review of 26 studies and meta-analysis of 7 studies (3,065 patients), prophylactic antibiotics reduced the relative risk of wound infection by 81% with an absolute risk reduction of 8%\textsuperscript{,42}

A modifiable risk factor for acute kidney injury is the specific antibiotic used for prophylaxis. Multiple studies assessed the risk of acute kidney injury comparing regimens containing an aminoglycoside (typically gentamicin) with regimens lacking these agents\textsuperscript{,20–26}

In general, these studies found a significantly higher risk of acute kidney injury when gentamicin was used.

Challagundla et al\textsuperscript{24} found an incidence of acute kidney injury of 52% using RIFLE creatinine criteria in 52 patients receiving 8 g total of flucloxacillin plus 160 mg of gentamicin (120 mg if they weighed less than 60 kg) compared with 8% in 48 patients given cefturoxime (3 g total) and 14% in an additional 52 patients also given cefturoxime.

Johansson et al\textsuperscript{23} found an incidence of KDIGO creatinine-based acute kidney injury of 13% in 70 patients given dicloxacillin alone prophylactically compared with 27% given dicloxacillin and gentamicin, with a relative risk of 3.

Bell et al\textsuperscript{21}, in a large registry-based analysis from Scotland involving 7,666 elective orthopedic procedures, found that use of flucloxacillin 2 g plus a single dose of gentamicin 4 mg/kg was significantly associated with a 94% higher risk of acute kidney injury (KDIGO creatinine criteria) compared with a cefturoxime-based regimen, with absolute rates increasing from 6.2% to 10.8%.

Dubrovskaya et al\textsuperscript{120} and Ferguson et al\textsuperscript{,26} in contrast, found no increased risk with addition of gentamicin.

We recommend avoiding aminoglycosides for prophylaxis in primary lower-extremity total joint arthroplasty in patients at higher risk unless required for specific microbiologic reasons.

Vancomycin may also increase risk

Courtney et al\textsuperscript{19} assessed the risk of adding vancomycin to cefazolin for routine prophylaxis in a retrospective series of 1,828 total hip or knee arthroplasties and found a significantly higher rate of acute kidney injury, using AKIN criteria (13% vs 8%, odds ratio by multivariate analysis 1.82, \(P = .002\))\textsuperscript{,19}

Other agents shown to be effective in treating periprosthetic joint infections or complicated skin and soft-tissue infections with resistant organisms include daptomycin\textsuperscript{43} and linezolid.\textsuperscript{44} These nonnephrotoxic alternatives to vancomycin may be a consideration if prophylaxis for methicillin-resistant Staphylococcus aureus is deemed necessary in patients at risk for acute kidney injury.

PROSTHETIC JOINT INFECTIONS AND ANTIBIOTIC-LOADED CEMENT

Deep infection may complicate nearly 1% of total hip\textsuperscript{45} and 2% of total knee arthroplasties.\textsuperscript{46} Kurtz et al\textsuperscript{46} have projected that by 2030, infection will be the cause of two-thirds of the estimated 268,000 revision total knee arthroplasties and about half of the estimated 96,700 revision total hip arthroplasties.

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The most common method of treating a chronically infected replacement joint is a 2-stage procedure. First, the prosthesis is removed, all infected bone and soft tissue is debrided, and an antibiotic-loaded cement spacer is implanted. Systemic antibiotics are given concurrently, typically for about 6 weeks. After the infection is brought under control, perhaps 2 to 3 months later, the spacer is removed and a new joint is implanted with antibiotic-loaded cement. A 1-stage procedure may be an option in selected cases and would obviate the need for an antibiotic-loaded cement spacer.

Of obvious relevance to development of acute kidney injury is the choice and amount of antibiotics embedded in the cement used for spacers and in implantation. Very high antibiotic levels are achieved within the joint space, usually with little systemic absorption, although significant systemic exposure has been documented in some cases.

The polymethylmethacrylate cement used for these purposes comes in 40-g bags. Multiple bags are typically required per joint, perhaps 2 to 4.

The rate of elution of antibiotics is determined by several factors, including surface area, porosity, and the number of antibiotics. In general, elution is greatest early on, with exponential decline lasting perhaps 1 week, followed by slow, sustained release over weeks to months. However, several in vitro studies have indicated that only about 5% of the total antibiotic actually elutes over time.

Initially, multiple antibiotic-laden cement beads were used to fill the joint space, but this significantly limited function and mobility. Now, cement spacers are used, and they can be nonarticulating or articulating for maximal joint mobility. Although much greater antibiotic elution occurs from beads due to their high surface area-to-volume ratio, spacers still provide an adequate dose.

### ANTIBIOTIC-LOADED CEMENT: DOSAGE AND ELUTION CHARACTERISTICS

Antibiotic-loaded cement can be either low-dose or high-dose.

**Low-dose cement**
Low-dose cement typically consists of 0.5 to 1.0 g of antibiotic per 40-g bag of cement, usually an aminoglycoside (gentamicin or tobramycin) or vancomycin, and can be purchased premixed by the manufacturer. Such cement is only used prophylactically with primary total joint arthroplasty or revision for aseptic reasons, a practice common in Europe but less so in the United States. Some American authors propose antibiotic-loaded cement prophylaxis for patients at high risk, eg, those with immunosuppression, inflammatory cause of arthritis, or diabetes.

Vrabec et al, in a study of low-dose tobramycin-loaded cement used for primary total knee arthroplasty, found a peak median intra-articular tobramycin concentration of 32 mg/L at 6 hours, declining to 6 mg/L at 48 hours with all serum levels 0.3 mg/L or less (unmeasurable) at similar time points.

Sterling et al, studying primary total hip arthroplasties with low-dose tobramycin-loaded cement, found mean levels in drainage fluid of 103 mg/L at 6 hours, declining to 15 mg/L at 48 hours. Serum levels peaked at 0.94 mg/L at 3 hours, declining to 0.2 mg/L by 48 hours.

Although most of the antibiotic elution occurs early (within the first week), antibiotic can be found in joint aspirates up to 20 years later. We are unaware of any well-documented cases of acute kidney injury ascribable to low-dose antibiotic-loaded cement used prophylactically. One case report making this assertion did not determine serum levels of aminoglycoside.

**High-dose cement**
High-dose antibiotic-loaded cement typically contains about 4 to 8 g of antibiotic per 40-g bag of cement and is used in the treatment of prosthetic joint infection to form the spacers. The antibiotic must be mixed into the cement powder by the surgeon in the operating room.

There is no standard combination or dosage. The choice of antibiotic can be tailored to the infecting organism if known. Otherwise, gram-positive organisms are most common, and vancomycin and aminoglycosides are often used together. This particular combination will enhance the elution of both antibiotics when studied in vitro, a process termed “passive opportunism.” Other anti-

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The most common method of treating a chronically infected replacement joint is a 2-stage procedure.
Biotics in use include aztreonam, piperacillin, teicoplanin, fluoroquinolones, cephalosporins, and daptomycin, among others.

About 8 g of antibiotic total per 40-g bag is the maximum to allow easy molding.52 As an example, this may include 4 g of vancomycin and 3.6 g of tobramycin per 40 g. Given that 3 to 4 such bags are often used per joint, there is significant risk of systemic exposure.

Kalil et al60 studied 8 patients who received high-dose tobramycin-loaded cement to treat periprosthetic joint infections of the hip or knee and found that 7 had detectable serum levels (mean 0.84 mg/L, highest 2.0 mg/L), including 1 with a level of 0.9 mg/L on day 38; 4 of these 8 developed acute kidney injury by AKIN criteria, although other risk factors for acute kidney injury existed. Nearly all had concomitant vancomycin (3 to 8 g) added to the cement as well.

### TABLE 3

| Study | Joints | No. of patients | Antibiotics in spacer | Definition of AKI | Incidence of AKI | Risk factors for AKI | Comments |
|-------|--------|-----------------|-----------------------|-------------------|-----------------|---------------------|----------|
| Jung68 | Hip    | 82              | Vancomycin 4 g, Gentamicin 1 g/80 g | Undefined | 6% | Undefined | 2 required dialysis  |
| Hsieh52 | Hip    | 99              | Vancomycin, gentamicin, aztreonam, tobramycin | Rise in serum creatinine ≥ 0.5 mg/dL or ≥ 50% | 5% | Undefined | AKI attributed to systemic antibiotics  |
| Menge69 | Knee   | 84              | Vancomycin, tobramycin (variable doses) | Rise in serum creatinine ≥ 50% (to > 1.4 mg/dL) within 90 days | 17% | Related to dose of vancomycin (> 4 g) and tobramycin (> 4.9 g) in spacer | Not associated with systemic vancomycin or tobramycin |
| Gooding69 | Knee  | 115             | Vancomycin 1.5 g, Tobramycin 3.6 g | Undefined | 2% | Undefined |  |
| Springer71 | Knee | 36              | Vancomycin mean 10.5 g/spacer, Gentamicin mean 12.5 g/spacer | Rise in serum creatinine | 3% | Undefined |  |
| Noto72 | Hip, knee | 46           | Tobramycin mean 8.2 g/spacer, Vancomycin mean 7.6 g/spacer | > 50% rise in serum creatinine | 22% | All patients tested had detectable tobramycin levels (mean 3.3, range 0.1–19.8 mg/L) | No systemic tobramycin |
| Aeng73 | Hip, knee | 50           | Tobramycin mean 3.6 g/40 g, Vancomycin mean 1.5 g/40 g | AKIN | 20% | Cement premixed with gentamicin, intraoperative transfusion, NSAIDs | No difference in antibiotic dose in cement with AKI |
| Geller74 | Hip, knee | 247          | Vancomycin with tobramycin or gentamicin, Vancomycin mean 5.3/40 g, Tobramycin mean 5.2/40 g, Gentamicin mean 1.3/40 g | KDIGO | 26% | BMI, lower preoperative hemoglobin, decrease in hemoglobin, comorbidity | Not related to dose of vancomycin in spacer |
| Reed75 | Hip, knee, shoulder, digits (306 non-dialysis) | 313 | Vancomycin median 1 g and/or tobramycin (median 1.2 g) in all but 1 | RIFLE | 9% (26/306) | ACEI exposure within 7 days, piperacillin-tazobactam within 7 days | 109 hip or knee AKI not related to dose in spacer |
| Yadav81 | Hip, knee | 197          | Vancomycin and tobramycin | RIFLE | 29% | Age, Charlson comorbidity index score, modest renal impairment |  |

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**Notes:**

- Two studies (Chohfi et al50 and Forsythe et al77) used antibiotic-loaded cement in primary arthroplasty, not in a spacer for treatment of infected joints.
- Dosages expressed as grams per 40-g bag of cement, grams per spacer, grams per 80 g of cement, or not specified.

ACEI = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; BMI = body mass index; KDIGO = Kidney Disease Improving Global Outcomes; NSAID = nonsteroidal anti-inflammatory drug; RIFLE = risk, injury, failure, loss, end-stage renal disease.
FILIPPONE AND YADAV

Hsieh et al studied 46 patients with infected total hip arthroplasties treated with high-dose antibiotic-loaded cement spacers (vancomycin 4 g and aztreonam 4 g per 40-g bag) and found vancomycin levels in joint drainage higher than 1,500 mg/L on day 1, decreasing to 571 mg/L on day 7; serum levels were low (range 0.1–1.6 mg/L at 24 hours), falling to undetectable by 72 hours.

ANTIBIOTIC-LOADED CEMENT SPACERS AND ACUTE KIDNEY INJURY

Case reports have associated high-dose antibiotic-loaded cement spacers with acute kidney injury.

Curtis et al described an 85-year-old patient with stage 3 chronic kidney disease who was treated for an infected total knee arthroplasty with an antibiotic-loaded cement spacer (containing 3.6 g of tobramycin and 3 g of cefazolin per 40-g bag, 3 bags total) and developed stage 3 acute kidney injury. After 16 days and 3 hemodialysis sessions, the patient's serum tobramycin level was still 2 mg/L despite receiving no systemic tobramycin.

Wu et al reported a case of acute kidney injury that required dialysis after implantation of a tobramycin- and vancomycin-loaded spacer, with persistent serum tobramycin levels despite repeated hemodialysis sessions until the spacer was removed.

Chalmers et al described 2 patients with acute kidney injury and persistently elevated serum tobramycin levels (3.9 mg/L on day 39 in 1 patient and 2.0 mg/L on day 24 in the other patient) despite no systemic administration.

In these and other case reports, dialysis and spacer explantation were usually required.

Comment. It is intuitive that acute kidney injury would more likely complicate revision total joint arthroplasties for infection than for primary total joint arthroplasties or revisions for aseptic reasons, given the systemic effects of infection and exposure to nephrotoxic or allergenic antibiotics. And the available data suggest that the risk of acute kidney injury is higher with revision for prosthetic joint infection than with revision for aseptic reasons. However, many of the studies were retrospective, relatively small, single-center series and used different definitions of acute kidney injury.

We are aware of 17 studies specifically addressing acute kidney injury or postoperative complications in general that may have included acute kidney injury. Ten of these studies found at least 1 case of acute kidney injury (Table 3). Of note, 7 studies totaling 219 patients reported no cases of acute kidney injury, although acute kidney injury per se was not mentioned and no definition of it was provided.

Luu et al performed a systematic review of studies published between January 1989 and June 2012 reporting systemic complications (including acute kidney injury) of 2-stage revision arthroplasties including placement of an antibiotic-loaded cement spacer for treatment of periprosthetic joint infection. Overall, 10 studies were identified with 544 total patients. Five of these studies, with 409 patients, reported at least 1 case of acute kidney injury for a total of 27 patients, giving an incidence of 6.6% in these studies. The remaining 5 studies, totaling 135 patients, did not report any cases of acute kidney injury, although that was not the primary focus of any of those trials.

Most notable from this systematic review, the study of Menge et al retrospectively determined the incidence of acute kidney injury (defined as a 50% rise in serum creatinine to > 1.4 mg/dL within 90 days of surgery) to be 17% in 84 patients with infected total knee arthroplasties treated with antibiotic-loaded cement spacers. A mean of 3.5 bags of cement per spacer were used in the 35 articulating spacers, compared with 2.9 per nonarticulating spacer. These spacers contained vancomycin in 82% (median 4.0 g, range 1–16 g) and tobramycin in 94% (median 4.8 g, range 1–12 g), among others in small percentages. The dose of tobramycin in the spacer considered either as a dichotomous variable (> 4.8 g, OR 5.87) or linearly (OR 1.24 per 1-g increase) was significantly associated with acute kidney injury, although systemic administration of aminoglycosides or vancomycin was not.

Additional single-center series that were published subsequent to this review have generally used more current diagnostic criteria.

Noto et al found that 10 of 46 patients
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As in Menge et al, this study illustrates the wide range of antibiotic dosages in use and the lack of standardization. In contrast to the study by Menge et al, however, development of acute kidney injury was not related to the amount of vancomycin or tobramycin contained in the spacers. Eventual clearance of infection (at 1 and 2 years) was significantly related to increasing amounts of vancomycin. Multiple different systemic antibiotics were used, most commonly vancomycin (44%), and systemic vancomycin was not associated with acute kidney injury.

Yadav et al, in a study of 3,129 consecutive revision procedures of the knee or hip, found an incidence of acute kidney injury by RIFLE creatinine criteria of 29% in the 197 patients who received antibiotic-loaded cement spacers for periprosthetic joint infection compared with 3.4% in the 2,848 who underwent revision for aseptic reasons. In 84 patients with prosthesis joint infection having various surgeries not including placement of a spacer, the acute kidney injury rate at some point in their course was an alarmingly high 82%. In the group that received spacers, only age and comorbidity as assessed by Charlson comorbidity index were independently associated with acute kidney injury by multivariate analysis. Surprisingly, modest renal impairment was protective, possibly because physicians of patients with chronic kidney disease were more vigilant and took appropriate measures to prevent acute kidney injury.

Overall, the risk of acute kidney injury appears to be much higher during treatment of prosthetic joint infection with a 2-stage procedure using an antibiotic-loaded cement spacer than after primary total joint arthroplasty or revision for aseptic reasons, and may complicate up to one-third of cases.

■ REDUCING RISK DURING TREATMENT OF INFECTED REPLACEMENT JOINTS

Due to lack of appropriate data, how best to mitigate the risk of acute kidney injury is uncertain. In our opinion, however, the following measures should be considered (Table 4).

As in primary total joint arthroplasty in general, higher-risk cases should be identified based on age, body mass index, chronic kidney disease,
comorbidities (hypertension, diabetes, established cardiovascular disease), and anemia.

Preoperative transfusion can be considered case by case depending on degree of anemia and associated risk factors.

All renin-angiotensin-aldosterone system inhibitors should be withheld starting 1 week before surgery.

Both nonselective and cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs should be avoided, if possible.

Strict attention should be paid to adequate intraoperative and postoperative fluid resuscitation.

Kidney function should be monitored closely in the early postoperative period, including urine output and daily creatinine for at least 72 hours.

Systemic administration of potentially nephrotoxic antibiotics should be minimized, especially the combination of vancomycin with piperacillin-tazobactam. Daptomycin is a consideration.

If acute kidney injury should develop, serum levels of vancomycin or aminoglycosides should be measured if the spacer contains these antibiotics. The spacer may need to be removed if toxic serum levels persist.

**TAKE-HOME POINTS**

Acute kidney injury may complicate up to 10% of primary lower-extremity total joint arthroplasties and up to 25% of periprosthetic joint infections treated with a 2-stage procedure including placement of an antibiotic-loaded cement spacer in the first stage.

Risk factors for acute kidney injury include older age, obesity, chronic kidney disease, and overall comorbidity. Potentially modifiable risk factors include anemia, perioperative transfusions, aminoglycoside prophylaxis, perioperative renin-angiotensin system blockade, and postoperative nonsteroidal anti-inflammatory drugs. These should be mitigated when possible.

In patients with periprosthetic joint infection who receive antibiotic-loaded cement spacers, especially patients with additional risk factors for acute kidney injury, strict attention should be paid to the dose of antibiotic in the spacer, with levels checked postoperatively if necessary. Nonnephrotoxic antibiotics should be chosen for systemic administration when possible.

Prospective randomized controlled trials are needed to guide therapy after total joint arthroplasty, and to verify the adverse long-term outcomes of acute kidney injury in this setting.

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