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# Single vs 2-Stage Revision for the Treatment of Periprosthetic Joint Infection

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ABSTRACT

Periprosthetic joint infection (PJI) is one of the most devastating complications following total joint arthroplasty, accounting for a projected 10,000 revision surgeries per year by 2030. Chronic PJI is complicated by the presence of bacterial biofilm, requiring removal of components, thorough debridement, and administration of antibiotics for effective eradication. Chronic PJI is currently managed with single-stage or 2-stage revision surgery. To date, there are no randomized, prospective studies available evaluating eradication rates and functional outcomes between the 2 techniques. In this review, both treatment options are described with the most current literature to guide effective surgical decision-making that is cost-effective while decreasing patient morbidity.



Periprosthetic joint infection (PJI) continues to be one of the leading causes of revision surgery and can be associated with a high morbidity and mortality [1]. Not only does this have a significant impact on a patient's physical and mental health, it also costs the healthcare system between $60,000 and $100,000 per episode [2,3].The incidence of PJI remains between 1% and 3% [4] in primary and 3% and 10% in revision arthroplasty [3,5]. The number of PJIs is projected to increase to almost 10,000 cases per year by 2030 [5].

Treatment of PJI is based on several factors including the timing of symptoms, the infecting organism, and health of the host and involves techniques such as irrigation and debridement with implant retention for acute infections and a 2-stage exchange arthroplasty or single-stage exchange arthroplasty for the treatment of chronic PJI. The goal of PJI treatment is to eradicate infection and maintain function of the limb. Due to the increased burden of PJI, the main priority should be to practice treatment options that have acceptable results and are safe, in the most cost-efficient manner.

The gold standard in the United States for the treatment of chronic PJI is a 2-stage exchange arthroplasty [6,7]. This treatment option involves 2 separate procedures separated by an interval with a temporary antibiotic spacer placement and intravenous antibiotic treatment. The reported success rates in the literature have varied between 65% and 95% depending on how successful the treatment is defined and the length of follow-up. For example, many studies have chosen to exclude patients who died before 2 years of follow-up. However, Berend et al [8] recently reported a strikingly high overall mortality rate of 7% before reimplantation and a 4% 90-day mortality rate following the first stage, calling into question what is and what is not a success for the patient.

As a result, alternative options such as single-stage revision as originally described by Buchholz et al [9] have become increasingly popular among surgeons who have traditionally performed 2-stage exchanges. A single-stage revision is an attractive option as it avoids a second surgery and is associated with decreased hospitalization and potentially lower costs to the healthcare system, assuming the success rates at least approach those of a 2-stage exchange. This procedure involves a thorough operative debridement including removal of the infected prosthesis and any associated infected soft-tissue and bone followed by implantation of a new prosthesis in one surgical setting [10,11]. To date, there are no prospective, randomized trials published comparing 1-stage vs 2-stage revision for PJI. The most recent systematic review and meta-analysis comparing the 2 treatment options have shown no difference in reinfection rates in both knees [12] and hips [13].

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The purposes of this review are to describe the advantages and disadvantages of single-stage vs 2-stage exchange arthroplasty for chronic PJI, identify pertinent indications for both procedures, and evaluate outcomes, infection eradication, and cost comparison from the most current literature.

### *Periprosthetic Joint Infection Diagnosis*

Suspicion for PJI should be noted for any patient with a painful arthroplasty. Currently, Musculoskeletal Infection Society criteria is the gold standard for infection diagnosis. Clinical suspicion for PJI should be high and we routinely obtain an erythrocyte sedimentation rate and C-reactive protein (CRP) as they are inexpensive screening tools with high sensitivity [14–16]. However, if clinical suspicion is high, joint aspiration should be performed even if these markers are normal. Synovial fluid obtained should be sent for a synovial fluid white blood cell (WBC) count, differential, and aerobic and anaerobic cultures [17]; fungal and acid-fast bacillus cultures are only sent if initial cultures are negative but other laboratory tests suggest PJI as routinely ordering these tests is low yield in our experience. There are many reports in literature attempting to define cutoff values for WBC count and percent polymorphic neutrophils (PMN) [18–27] in chronic PJI. The International Consensus on PJI recommends thresholds of WBC >3000 cells/μL and %PMN of 80% [28].

The variation in cutoff values and diagnostic accuracy for synovial WBC and %PMN throughout literature and desire for a single diagnostic reference test have increased interest in discovering other synovial and genetic markers that may improve PJI detection. Deirmengian et al [29] reported a sensitivity of 0.97 and specificity of 1.0 using a combination of synovial alpha-defensin and synovial CRP in joint aspirates from 112 patients with aseptic failure and 37 with PJI. New techniques involving DNA sequencing may improve diagnostic value for PJI especially with culture-negative infections. In a prospective study by Tarabichi et al [30], next-generation sequencing detected pathogens in 80% of culture-negative PJIs. However, this technology also detected pathogens in 35% of primary TJA and 25% of revision TJA in patients who were considered noninfected by Musculoskeletal Infection Society criteria [30].

Patients who present less than 3 weeks from index surgery or symptom onset, debridement and implant retention is the preferred treatment at our institutions. For chronic (>3 weeks), consideration to single-stage vs 2-stage exchange arthroplasty is the preferred method and will be described below in detail.

### *Single-Stage Exchange Arthroplasty*

Single-stage revision is becoming a more popular option as data continue to show noninferior outcomes compared to a 2-stage exchange [31–33]. After a meticulous surgical debridement, at our high-volume tertiary referral centers we use a completely new setup with clean drapes and instruments to place the revision components. As previously described, the primary advantage is that explantation and reimplantation is performed in a single procedure and hospitalization. While the indications and contraindications for a single-stage exchange continue to evolve, in general strict exclusion criteria include culture-negative infections and significant soft tissue loss that would preclude primary closure of the wound. Relative contraindications include antibiotic-resistant organisms and the presence of a sinus tract [34,35]. Criteria for single-stage exchange arthroplasty are summarized in Table 1.

Overall, the majority of current evidence does not support improved function in single-stage exchange over a 2-stage revision. Haddad et al [32] did, however, report significantly increased Knee Society Scores in single-stage exchange (88 vs 76, $P < .001$) in 102 patients with a mean follow-up of 6.2 years. Due to the complexity of multiple variables in PJI including organism type, bone stock, and host grade, results from single-stage studies may be not be directly comparable to 2-stage exchange as there is a selection bias toward healthier patients with good bone stock and less-virulent organisms to receive a single-stage exchange.

When treating an infected THA, there is substantial controversy around the use of implants that are fully cemented into place or whether cementless implants can be used. Historically, proponents of a 1-stage exchange have espoused that the use of cement to deliver local antibiotics was critical to the success of the procedure. Antibiotics elute through pores in the cement and follow a concentration gradient into local tissue and bone [39]. The goal is to obtain minimal inhibitory concentrations above 100×-1000× to effectively disrupt biofilms [39]. However, the amount of time needed at this level has yet to be determined despite evidence showing local levels dropping below 100× minimal inhibitory concentration within a few days [39]. Common water-soluble powder forms of antibiotics used in cement for broad-spectrum coverage include a combination of tobramycin, gentamicin, cefazolin, vancomycin, and cefoxitin. For fungal infections, amphotericin B or fluconazole can be used. Although this allows high concentration of antibiotics at the source of the infection, mechanical properties of cement are dampened, increasing risk of failure [40]. However, the experience with using fully cemented components for revisions in North America has been poor despite excellent results reported in Europe [41,42] with most high-volume revision surgeons routinely using cementless implants for their reconstructions and this has been among the factors that have led to a more limited use of a single-stage exchange [43,44].

More recent studies have suggested that a 1-stage exchange for a hip PJI can be performed successfully, challenging the notion that antibiotic-loaded cement is required for a single-stage technique. Cementless single-stage exchange for an acute infection is performed with success rates ranging from 70% to 83% [45,46]. In the chronic setting, cementless single-stage revisions have been reported to have eradication rates up to 83.3% (10/12) with 7-year follow-up [47]. However, this study excluded patients with

**Table 1**
Criteria for Single-Stage Exchange Arthroplasty.

| International Consensus Meeting [35] | Infectious Diseases Society of America [36] | University College of London Hospital [37] | ENDO-Klinik [38] |
|---|---|---|---|
| Organism identified preoperatively<br>Organism susceptible to antibiotics | Organism identified preoperatively<br>Organism susceptible to antibiotics with oral bioavailability<br>Good soft tissue<br>Good bone stock<br>Bone grafting not required<br>Antibiotic-loaded bone cement used for fixation | Organism identified preoperatively<br>Organism susceptible to antibiotics<br>Good soft tissue | Organism identified preoperatively<br>Organism susceptible to antibiotics |

**Table 2**
Recent Published Results on Single-Stage Exchange Arthroplasty.

| Single-Stage Exchange | | | | | |
|---|---|---|---|---|---|
| First Author/Year | Location | Subjects | Mean Follow-Up (y) | Eradication Rate (%) | Functional Score |
| Ji, 2019 [33] | Hip-cementless | 111 | 58 mo | 89.2 | HHS 79.9 |
| Siddiqi, 2019 [54] | TKA | 57 | 52.9 mo | 86 | — |
| Zahar, 2018 [52] | Hip-cemented | 85 | 10-11 | 94 | HHS 75 |
| Bori, 2018 [31] | Hip-cementless | 19 | | 94.7 | — |
| Lange, 2017 [48] | Hip-cementless | 56 | 4 | 91.1 | OHS 35.1 |
| Whiteside, 2017 [55] | Hip-cementless | 21 | 5.2 | 95 | — |
| Born, 2016 [56] | Hip-cementless | 28 | 7 | 100 | — |
| Choi, 2013 [51] | Hip | 17 | 5.1 | 82 | — |
| Rudelli, 2008 [57] | Hip | 32 | 5 | 94 | — |
| Callaghan, 1999 [58] | Hip | 24 | 10 | 92 | — |
| Ebied, 2017 [59] | Hip | 33 | 6 | 97 | — |
| Ilchmann, 2016 [60] | Hip | 39 | 6.6 | 100 | — |
| Kunutsor, 2015 [49] | Knee | 423 | — | 90.1 | 80.3 KSS |
| Haddad, 2015 [32] | Knee | 28 | 6.5 | 100 | — |
| Tibrewal, 2014 [61] | Knee | 50 | 10.5 | 98 | — |
| Buechel, 2004 [62] | Knee | 22 | 10 | 91 | — |
| Silva, 2002 [63] | Knee | 37 | 5 | 89 | — |

TKA, total knee arthroplasty; HHS, Harris Hip Score; OHS, Oxford Hip Score; KSS, Knee Society Score.

methicillin-resistant *Staphylococcus aureus* infections. Recently, Lange et al [48] reported a 91% infection-free rate at an average follow-up of 35.1 months in 53 patients following cementless single-stage revision for chronic infection.

Overall, outcomes using single-stage exchange have been satisfactory and noninferior to 2-stage exchange arthroplasty [13,49–51]. Zahar et al [52] recently reported 94% eradication rate with 75.9% surgery-free survival rate at 10-year follow-up in cemented THA with an average 41-point improvement in Harris Hip Scores. Raut et al revealed 84% eradication rate [53] and 86% eradication rate in patients with sinus tracts [10] at 7-year follow-up in THA. As for TKA, Siddiqi et al [54] recently reported an 86% eradication rate and 80.7% surgery-free survival rate at 5-year follow-up in patients receiving cemented all-polyethylene tibia components. Table 2 lists current studies on outcomes following single-stage exchange.

The trend for single-stage revision surgery for PJI appears to be increasing due to the inherent advantages mentioned earlier; however, it is extremely difficult to interpret data as this procedure tends to be performed in healthier patients with better bone stock and less-virulent organisms. Eradication rates and functional scores are thus inherently high if not better than those reported for 2-stage exchange [33,48,52,56]. Furthermore, mortality at 10 years has been reported at 30.3% [52] compared to 15% at a mean 8.6-year follow-up [64] and 48% at a mean 15-year follow-up [8] in patients treated with 2-stage protocol.

### *Two-Stage Exchange Arthroplasty*

As opposed to single-stage exchange arthroplasty, a 2-stage exchange arthroplasty involves 2 separate procedures. The first surgery involves a thorough debridement and removal of infected implants and associated foreign material and soft tissue with the placement of an antibiotic-loaded bone cement (ALBC) spacer. This is followed by an interval period of intravenous and/or oral antibiotic administration until the infection is clinically eradicated before the second procedure involving removal of the spacer and reimplantation of a new prosthesis. Six weeks of parenteral antibiotics is typically recommended during the interstage period [65]; however, evidence is lacking on duration. Admittedly, one of the challenges however has been determining reliably and objectively when the prior infection has been eradicated and when the second-stage procedure can or should be performed. While several different protocols have been described and many surgeons state that they monitor the trend of the erythrocyte sedimentation rate and CRP over time, it has been challenging to delineate objective cut-off values [66–68]. This has prompted investigators to look at alternative markers such as Kheir et al [68] who reported a specificity of 1.0, but only a sensitivity of 0.23 using leukocyte esterase strip for PJI before reimplantation. Recently, alpha-defensin showed poor sensitivity of 7% and accuracy of only 73% in detecting infection eradication 1 year out before reimplantation for 2-stage revision [69]. To date, there is no single reliable diagnostic test for persistent infection and optimal timing before reimplantation for 2-stage revision.

The results of this technique were first described by Phillip Nelson in 1 patient in 1977 [70] and has become the gold standard for treatment of chronic periprosthetic joint infection in the United States [6]. The most critical aspect of this surgical method regardless of technique is a thorough debridement. This should include removal of all implants and hardware, nonviable tissue and debris, and sinus tracts with copious amounts of saline irrigation to dilute bacterial load. Different antiseptic agents for irrigation of the wound bed have also been studied recently, but further prospective studies comparing all chemical antiseptic agents are needed to determine the optimal solution [71–73].

Two universally used techniques for 2-stage revision involves the placement of a static or articulating ALBC spacer (Fig. 1). The primary goal of both types of spacers is to safely deliver adequate concentrations of antibiotics over an extended period of time throughout the surrounding bone and soft tissue to eradicate infection. Heat-stable antibiotics with low serum binding such as tobramycin, gentamycin, and vancomycin are most commonly used. Doses ranging from 2 g to 8 g of antibiotic per 40-g bag of cement have been shown to be safe while maintaining adequate elution kinetics at therapeutic levels [74–76]. Although there is no standardized antibiotic dosing regimen for spacers, 2-4 g of vancomycin combined with 2.4-4.8 g of tobramycin [77] or 4.8 g of gentamicin [76] per 40-g bag of cement appears safe and sufficient. Lower-dose ranges are typically used for high-viscosity cements as it tends to elute more antibiotics than lower-viscosity cement [78]. More importantly, antibiotics should be selected based on sensitivities if available before spacer placement.

Static spacers consist of various constructs of ALBC that fill the voided space created by the removal of implants of the hip or knee. Static spacers are generally manually molded ALBC with subsequent insertion into the femoral canal (and tibial canal for knees) and may include molding ALBC around a supportive endoskeleton such as

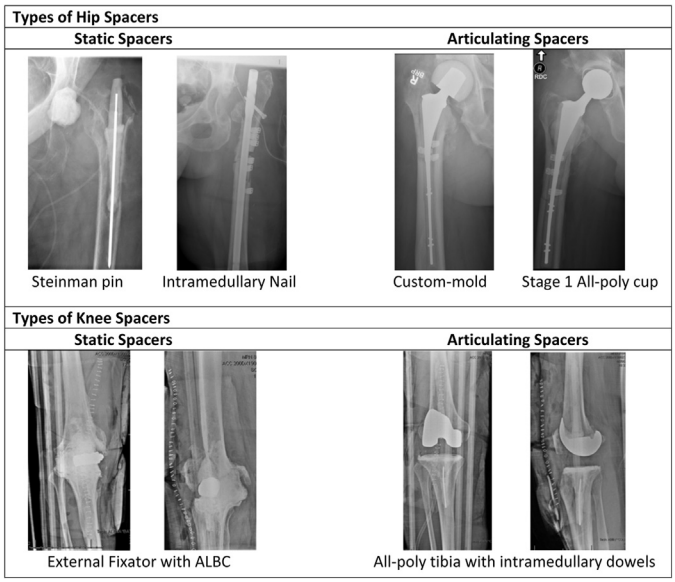


**Fig. 1.** Types of spacers used in 2-stage revision arthroplasty for periprosthetic joint infection. Poly, polyethylene; ALBC, antibiotic-loaded bone cement.

Steinman pins or an intramedullary nail for structural support. Static spacers are favorable in scenarios with significant bone loss and/or abductor deficiency for the hip or extensor mechanism disruption in the knee where an articulating spacer may be at risk of fracture and dislocation [79]. Because structural support is not of significant importance, ALBC can be composed with high porosity and adequate antibiotic coverage to improve elution profile.

Articulating spacers consist of constructs that allow for joint mobility and maintenance of leg length for both hips and knees. These can include handmade articulating spacers, prefabricated spacers, spacer molds, or the use of real components that are fashioned and coated with high-dose antibiotic cement. These spacers are preferred by many surgeons as there have been good functional outcome scores and notable increased quality of life before reimplantation [80,81]. While there is no definitive indication to use static vs articulating spacers, articulating spacers are not favored in the setting of significant bone loss, and/or abductor deficiency of the hip or extensor mechanism deficiency in the knee. Handmade and custom-molded spacers have excellent infection-free rates of 89%-100% with a low risk of fracture or dislocation [82–84]. While these options may be cost-effective, limited mold sizes and cemented heads articulating against native acetabular geometry can lead to pain, acetabular erosion, and dislocation. Preformed spacers are similar in shape and articulation to custom-molded spacers but contained a predetermined amount and type of antibiotic. Consequently, antibiotic treatment is difficult to tailor toward certain infections with this spacer despite excellent reports on infection eradication [85]. In a large literature review, Citak et al [86] noted no difference in functional outcome with similar eradication rates comparing surgeon-molded vs preformed implants. However, a significant higher rate of fracture was documented in the surgeon-molded spacers. Lastly, metal-on-cemented polyethylene implants have been used with great success. Hofmann et al [87] report a technique using a resterilized femoral stem with cemented polyethylene liner demonstrating an infection eradication rate of 94% on 42 hips with average 76-month follow-up. The prosthesis of antibiotic-loaded acrylic cement (PROSTALAC; Depuy Synthes, Warsaw, IN) consists of a custom-molded stem with modular head into a semiconstrained polyethylene liner. This implant construct has several studies with reported success rates from 82.8% to 96% [80,88,89].

To date, there are no studies comparing static vs articulating hip spacers. These studies remain difficult to conduct as there are a wide variety of factors including spacer technique, antibiotic type and concentration, type of cement, duration of spacer placement, and species of bacteria that are near impossible to control especially for a randomized trial. Reports on static spacers show rates of reinfection from 1.4%-8% without any reported dislocations or fractures [90–93]. Among all types of articulating spacers, reinfection rates for studies including over 50 hips is between 1.7% and 10.7% with dislocation rate between 3.4% and 4.4% and fracture rate of 1.5%-3.4% [89,90,94]. Refer to Table 3 for studies on outcomes following 2-stage exchange.

Despite the obvious advantages of 2-stage revision including 2 chances at thorough debridement, interval period of antibiotics in between stages, and historically high eradication rates and functional outcome scores, there are some important risks [49,95]. This process subjects a patient to 2 major operations. Interval time in between stages can be debilitating especially in patients with static spacers. This can lead to increased immobilization and time in skilled nursing or rehab facilities. As well, complications such as spacer failure can lead to further surgery and morbidity. Gomez et al reported that 18% of patients were unfit for the second-stage procedure and a 10.3% mortality rate within 2 years, indicating the high morbidity rate during the interim of 2-stage exchange.

### *Cost*

Two-stage exchange has been associated with higher direct healthcare costs; however, comparison between the 2 techniques can be difficult due to multiple factors including but not limited to the cost of implants, antibiotics, operative room time, facility fees, and patient comorbidity. A retrospective cost analysis by Merollini

**Table 3**
Recent Results of 2-Stage Exchange Arthroplasty.

| Two-Stage Exchange | | | | | |
|---|---|---|---|---|---|
| First Author/Year | Location | Subjects | Mean Follow-Up (y) | Eradication Rate (%) | Functional Score |
| Matar, 2019 [95] | Hip-cemented | 29 | 5 | 96.5 | 76 HHS |
| Siddiqi, 2019 [54] | Knee | 137 | 54.7 mo | 75.9 | — |
| Di Benedetto, 2017 [96] | Knee | 45 | 3.4 | 89.9 | — |
| Kunutsor, 2016 [49] | Knee | 5129 | — | 87.8 | 82.1 KSS |
| Haddad, 2015 [32] | Knee | 74 | 6.5 | 93 | 76 KSS |
| Sabry, 2014 [97] | Knee | 314 | — | 66.6 | — |
| Kubista, 2012 [98] | Knee | 368 | 3.5 | 86 | — |
| Mahmud 2012 [99] | Knee | 253 | 4 | 95.7 | — |
| Mortazavi, 2010 [100] | Knee | 475 | 5.5 | 90.7 | — |
| Ghanem, 2009 [101] | Knee | 109 | — | 88.9 | — |

HHS, Harris Hip Score; KSS, Knee Society Score.

et al estimated over 50% increased cost in 2-stage over single-stage revision for PJI [102]. Klouche et al [103] estimated 2-stage exchange for hips to be about 1.7 times higher than single-stage in France. In an era focusing on cost containment, single-stage exchange seems appealing, however it should not direct surgical decisions if the criteria for this method are not met.

*Postoperative Management*

The use of antibiotics after a single-stage exchange should be tailored to the organism sensitivities. The duration of antibiotic treatment described in the literature, however, varies widely from 2 weeks [104] to 3 months or more [105]. Similarly, antibiotic administration following successful 2-stage revision remains controversial at this time. In a large, multicenter, randomized, controlled trial, Frank et al [106] revealed a decreased failure rate from infection (5% [3/59] vs 19% [9/48]) in patients who received 3 months of oral antibiotics following second-stage reimplantation. Coordination with an infectious disease specialist may be crucial in antibiotic selection, duration, and side-effect monitoring.

*One-Stage vs 2-Stage*

Single-stage exchange has similar reported infection eradication rates compared to a 2-stage exchange; however, no direct randomized studies exist at this time directly comparing the 2 regimens [49–51]. In a systematic review by Leonard et al [50], single-stage procedure offers similar success rates with a trend toward better functional outcomes compared to 2-stage revision. Kunutsor et al [49] report a reinfection rate of 8.2% for single-stage and 7.9% for 2-stage revisions for PJI in a large meta-analysis. Similarly, Choi et al [51] report better but not statistically significant infection control (82% vs 75%) and functional outcome (Harris Hip Score of 77 vs 60) in one-stage vs 2-stage revision in 83 patients. Despite obtaining pooled data with recent systematic reviews and meta-analysis, there are many limitations when interpreting this data. Most meta-analysis are comprised of level IV retrospective studies. There tends to be significant loss to follow-up in this patient cohort as well as tendency to perform 2-stage exchange on patients who have poorer host bone or have more virulent infections which result in selection bias. Additionally, different protocols exist among institutions regarding technique of debridement, spacer choice, and reimplantation as well as the definition or diagnostic tools used to indicate infection eradication. Because of the stark differences between the 2 techniques regarding length of hospitalization and cost, prospective randomized trials with standardized protocols that significantly reduce bias are needed to direct patient care in eradicating infection and improving function.

## Conclusions

Periprosthetic joint infection remains a devastating complication. The shortcomings of the current literature fail to provide superiority of either the single-stage exchange or 2-stage exchange. There is a rising popularity of the single-stage exchange in North America based on recent literature demonstrating comparable success, potential functional benefits to the patients, and a decreased burden to the healthcare system. Large, randomized, controlled, comparative trials are needed to assist us in determining the best treatment option for these patients. A shared-decision model should be discussed with the patient regarding treatment options for chronic PJI.

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