Review Article

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Two-Stage Reimplantation in Infected Total Knee Arthroplasty

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Two-stage reimplantation is considered the gold standard for the management of periprosthetic joint infection. The first stage involves the removal of the prosthesis, followed by extensive debridement of all nonviable tissues, synovectomy, irrigation, and reaming of the medullary canals. Once the joint has been prepared, antibiotic-impregnated cement beads and/or spacer are inserted. Antibiotic-impregnated spacers are now more commonly used, and an increasing number of orthopaedic surgeons are using articulating spacers if indicated. Antibiotics are then prescribed to the patient based on the sensitivities of the infecting organism. The duration of systemic antibiotic use is decreasing, and short courses of antibiotic therapy have been shown to be as efficacious as prolonged therapy between the first and second stages. The second stage of the procedure involves removal of the antibiotic-impregnated cement beads and/or spacer, repeat irrigation and debridement, and final reconstruction with revision components. While two-stage reimplantation was considered the gold standard in many parts of the world, recent studies have demonstrated that it is associated with a considerable failure rate. This may be due to the lack of accurate diagnostic tools for infection eradication, and future investigation of risk factors for failure of the two-stage reimplantation should be conducted.

Keywords: **Knee, Arthroplasty, Infection, Spacer, Antibiotics, Reimplantation**

Introduction

One of the most serious complications after total knee arthroplasty (TKA) is periprosthetic joint infection (PJI). Despite tremendous advances in the prevention, diagnosis, and treatment of PJI, it remains the most commonly reported cause of early failure in TKA, resulting in the need for subsequent revision[1-3]. The Musculoskeletal Infection Society (MSIS) developed diagnostic criteria to standardize and facilitate the diagnostic process (Table 1)[3]. The ultimate goal of the reimplantation procedure is to eradicate infection and reconstruct a functional, and stable joint with reduced pain. Treatment of PJI is not possible by antibiotics alone in most cases, and surgical interventions such as irrigation and debridement, one-stage reimplantation, two-stage reimplantation, resection arthroplasty, or amputations are required[4].

Most PJI patients require treatment by one- or two-stage reimplantation, but two-stage reimplantation was considered as the gold standard for the management of PJI[5]. One-stage revision (irrigation, debridement, and reimplantation performed during the same surgery) is limited to the following criteria: when the type of causative organism is known and is a sensitive gram-positive organism; antibiotic therapy for the causative organism can be administered for 12 weeks; the infection is not polymicrobial; and patient factors are optimal (e.g., adequate soft tissue envelop, adequate bone for reconstruction, and no immunosuppression or significant comorbidities)[6-9]. Therefore, in this review, we will provide an overview focused on two-stage reimplantation in the following order: definition and procedure, antibiotic-impregnated spacers, role and timing of systemic antibiotic administration, optimal timing of reimplantation, and outcomes.

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Table 1. Musculoskeletal Infection Society Diagnostic Criteria for PJI[a)]

One of the 3 following criteria must be met for the diagnosis of PJI
1. A sinus tract communicates with the prosthesis
2. A pathogen is identified on culture of ≥2 separate samples of periprosthetic tissue or fluid
3. Three of the five criteria below are present
1) Serum ESR and serum CRP concentration are elevated.
2) Synovial WBC count is elevated.
3) Synovial neutrophil percentage is elevated.
4) A microorganism is isolated in 1 periprosthetic tissue or fluid culture
5) >5 neutrophil per HPF in 5 HPFs are detected on histological analysis of periprosthetic tissue at 400×magnification

PJI: periprosthetic joint infection, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: white blood cell, HPF: high power field.
[a)]Modification by Parvizi et al.[3)]

Definition and Procedure

Two-stage reimplantation was first described by Insall et al.[10)]. The first stage involves the removal of the prosthesis, followed by extensive debridement of nonviable tissues (including synovectomy), irrigation, and reaming of the medullary canals. Once the joint is prepared, antibiotic-impregnated cement beads and/or spacer are inserted. Postoperatively, antibiotics are administrated based on the sensitivities of the infecting organisms. Reimplantaion is delayed until the antibiotic regimen is completed, the wound has healed, and infection treatment has been confirmed. The second stage of the procedure involves removal of the antibiotic-impregnated cement beads and/or spacer, repeating irrigation and debridement, and final reconstruction with revision components[8,10)].

Many tissue samples from different areas should be collected for microbiological examination, including intramedullary canals and posterior capsule. Extensive debridement is essential for both first and second stages, similar to tumor excision surgery. All septic membranes must be radically excised, and special care needs to be taken to debride the posterior capsule, since it is a potential source of reinfection. Removal of well-fixed components carries the risk of destruction of bone and adjacent soft tissues, and cortical windows may be required for the removal of well-fixed uncemented components. All efforts should be made to minimize bone loss[5)]. After debridement, copious amount of fluid should be used for irrigation. However, usefulness of pulsatile lavage and the most efficacious antimicrobial solution for irrigation remain inconclusive and unknown[5)].

Antibiotic-Impregnated Spacers (Articulating versus Static)

Antibiotics can be incorporated into bone cement because commercially available antibiotic-impregnated cement only contains prophylactic doses of antibiotics which are inadequate to manage infection. Appropriate antibiotics should be bactericidal, water soluble, and thermodynamically stable, allow gradual release over an appropriate period of time, and evoke minimal local inflammatory reaction[11)]. Typically, amikacin, ampicillin, cefazolin, ciprofloxacin, gentamicin, penicillin, and vancomycin can be used[8)]. Most importantly, the selection of antibiotics should be based on treating likely pathogens and accompanying culture sensitivities. The amount of antibiotics may be up to 20% of the total mass of the spacer (e.g., 2–4 g of vancomycin per 40 g bag of cement), since the mechanical strength of the spacer is not a major concern[5)]. However, care should be taken to avoid systemic toxicity such as acute kidney injury[12)]. A maximum of 10% by weight of antibiotic is generally recommended with a consideration of risk and benefit[13)].

Antibiotic-impregnated cement spacers can be inserted after irrigation and debridement. The goal of the spacer is to preserve the joint space and reduce soft tissue contracture while delivering high doses of antibiotics[5,14)]. Cement beads are also effective for providing a high local concentration of antibiotics; however, the joint is left in a state of pseudoarthrosis which can further complicate the second stage of the procedure[8,11,15)]. Spacers can be inserted in a static or dynamic form. Static spacers are inserted to provide joint stability, but they essentially create a temporary joint arthrodesis since no motion is allowed (Fig. 1). Articulating spacers were later introduced to enhance functional status, maintaining range of motion while improving patient satisfaction (Fig. 2)[16,17)].

Static spacers are generally recommended for cases with massive bone loss, lack of functional collateral ligaments, and the need for soft-tissue reconstruction. However, no clear contraindications have been described for the use of either type of spacer[5,18)]. While general functional improvement is expected with articulating spacers, the results for infection eradication are similar in individual studies. It is interesting that three systematic reviews were published in a similar time period (2013–2014)[17,19,20)] which all included a comparable number of articles that were similar. All three articles reported that articulating spacer groups had significantly higher range of motion (articulating vs. static spacer: 100° vs. 92°, 100° vs. 83°, 101° vs. 91°, respectively)[17,19,20)], although functional scores were similar in the two treatment groups. Re-

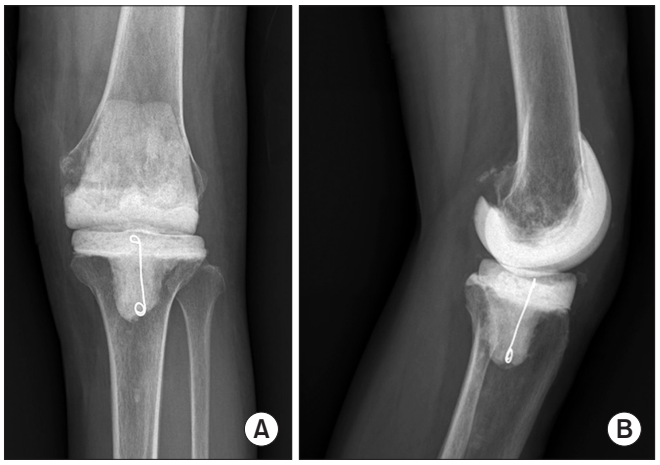

Fig. 1. The articulating spacer is molded according to the size of the resected femoral and tibial surfaces. (A) Anteroposterior view. (B) Lateral view.

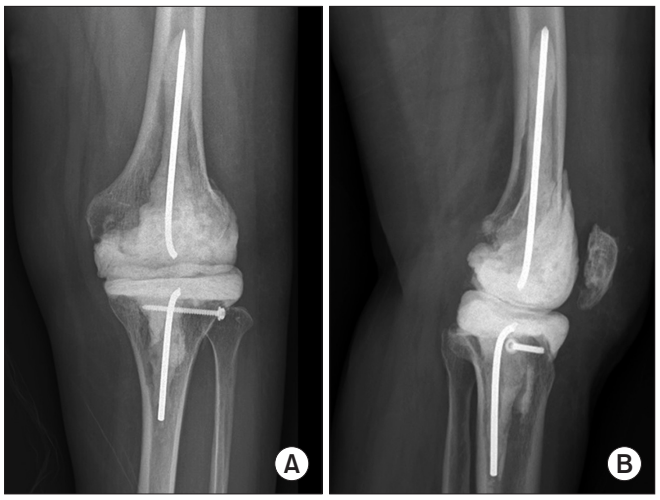

Fig. 2. A static spacer is inserted and it is augmented by intramedullary extension using a Steinmann pin or broken nail. (A) Anteroposterior view. (B) Lateral view.

garding reinfection rate, different interpretations exist. Pivec et al.[19] analyzed outcomes stratified into complex and simple cases, and reported no significant differences in reinfection, complication, or reoperation rates. However, Guild et al.[17] reported that articulating spacers showed a lower re-infection rate, facilitated reimplantation, and resulted in less bone loss than static spacers. Voleti et al.[20] reported no statistical difference in re-infection rate between the groups, although the mean reinfection was 12% for static spacers and 7% for articulating spacers, and six of the seven level III studies demonstrated greater reinfection rates in the static spacer group than in the articulating spacer group. None of the individual studies demonstrated a significant difference in infection eradication secondary to the overall paucity of reinfections.

Role and Timing of Systemic Antibiotics

When two-stage reimplantation was first introduced, prolonged delivery of intravenous antibiotics (commonly 6 weeks) was recommended[10]. The 1st and 3rd generation cephalosporins were recommended when *Streptococcus* was the causative organism. Vancomycin and rifampin combination therapy was recommended for *Streptococcus* or methicillin-resistant *S. epidermidis* infections, and aminoglycosides were recommended for gram-negative infections. This is often a significant cost to the patient and healthcare system. Additionally, the usefulness of 6 weeks of antibiotics is questionable since the blood supply to the periarticular tissue may become attenuated, preventing systemically administered antibiotics from reaching the desired site in the setting of infection and surgical trauma[8]. Meanwhile, intraarticular antibiotic-impregnated cement spacers can maintain antibiotic levels that are effective against infection for up to 4 months[13,21,22]. Some studies reported comparable results between a short course of intravenous antibiotics (2 weeks of use) and an extended period of use[23,24]. Hart and Jones[23] used articulating cement spacers and short-term parenteral antibiotic therapy in the postoperative period, and infection was successfully eradicated in 88% of patients. Whittaker et al.[24] used systemic vancomycin for two weeks in combination with a vancomycin- and gentamicin-eluting spacer system, and successful infection treatment occurred in 92.7% of patients. Hsieh et al.[21] compared outcome between prolonged (6 weeks) and short-term (1 week) antibiotic use in two-stage reimplantation in infected THA. In this study, infection control and outcomes were similar, but nephrotoxicity and neutropenia occurred in 5 patients who received prolonged antibiotic treatment. Currently, antibiotic treatment is recommended for 4–6 weeks after the first stage; however, the treatment should be individualized, taking into account the infecting organism and the patient. In the first 2 weeks, intravenous administration is recommended, after which oral treatment may be continued depending on the resistance profile of the organism and the availability of an appropriate agent[5,25]. Zywiel et al.[26] compared outcomes between patients who received prophylactic oral antibiotics (average 33 days) and 24–72 hours of intravenous antibiotics. This study suggests that the use of oral antibiotic prophylaxis following reimplantation may be appropriate in all patients undergoing two-stage revision, even in the absence of any signs of active infection.

Optimal Timing of Reimplantation

No single current investigation has accurately or reliably determined the successful eradication of infection after resection arthroplasty in two-stage reimplantation for PJI[5]. The international consensus on PJI established a complex algorithm to reach reliable diagnostic accuracy for PJI, and has shown that local proinflammatory cytokines have favorable diagnostic properties for PJI[27]. However, these designations were not designed for reimplantation and may not adequately detect resolution of infection in a joint previously treated with component explantation and placement of an antibiotic spacer[28]. Compared to primary arthroplasty, assessment of the infection eradication can be more difficult in the setting of reimplantation because patients have often been on prolonged antibiotic therapy and with placement of an antibiotic-impregnated cement spacer. The use of antibiotics can confuse the timing of infection clearance, as antibiotic-impregnated cement spacers can act as a scaffold on which biofilm formation may occur[29]. Current protocols remain inadequate to address the timing of two-stage reimplantation of PJI.

Clinicians often follow serial serum inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), but these tests have been reported to have low sensitivity (range, 0.29 to 0.78) (Table 2)[6,30-33]. The international consensus meeting on PJI demonstrated that local proinflammatory cytokines have favorable diagnostic properties for PJI and largely outperform established serum markers such as CRP and ESR[27,34-36]. However, these proinflammatory cytokines were not adequately evaluated in reimplantation. Preoperative aspiration prior to reimplantation is associated with a high percentage of false negatives. Synovial white blood cell (WBC) count, percentage of polymorphonuclear cell (%PMN), gram stain, and culture have also shown low and inconsistent sensitivities (range, 0.05 to 0.82) (Table 3)[30-33,37,38]. Currently, numerous synovial biomarkers are being evaluated as potential candidates[39]. Regarding tissue culture, Mont et al.[40] reported a sensitivity of 0.75 and a specificity of 1.00, while Williams et al.[41] reported a sensitivity of 0.83 and a specificity of 0.90. For synovial fluid %PMN, Kusuma et al.[31] reported a sensitivity of 0.75 and a specificity of 0.66; Shukla et al.[32] reported a sensitivity of 0.78 and a specificity of 0.82. Regarding synovial fluid culture, studies[30,33,37,41] reported a sensitivity of 0.36–0.80 and a specificity of 0.63–1. Other parameters had lower sensitivities and specificities. Regarding synovial fluid WBC count, studies[30-32] reported the sensitivity as 0.31–0.78 and the specificity as 0.39–0.96. Tissue culture, synovial fluid %PMN, and synovial fluid culture showed the greatest promise as markers to guide reimplantation, but we cannot provide a firm recommendation regarding the superiority of any one of those tests over others. Therefore, the current approach using multiple tools rather than a single marker is essential. Many authors have

Table 2. Diagnostic Value of the Serum Marker

Study	No.	Serum marker	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Kusuma et al.[31]	76	ESR	0.67	0.62	0.13	0.05	0.62	0.62
Shukla et al.[32]	86	ESR	0.78	0.69	0.23	0.04	0.7	0.76
Ghanem et al.[6]	109	>30, ESR	0.65 (0.427–0.836)	0.32 (0.22–0.44)	0.23 (0.14–0.35)	0.75 (0.6–0.9)		
		>45, ESR	0.46 (0.26–0.67)	0.51 (0.39–0.63)	0.23 (0.14–0.35)	0.75 (0.6–0.9)		
		△5, ESR	0.71 (0.49–0.87)	0.24 (0.14–0.35)	0.23 (0.14–0.35)	0.72 (0.51–0.88)		
		△10, ESR	0.67 (0.48–0.86)	0.25 (0.16–0.37)	0.22 (0.13–0.34)	0.7 (0.5–0.86)		
		△15, ESR	0.63 (0.41–0.81)	0.29 (0.19–0.4)	0.22 (0.12–0.32)	0.71 (0.52–0.86)		
Hoell et al.[30]	115	CRP	0.42	0.84	0.35	0.88		0.63
Kusuma et al.[31]	76	CRP	0.17	0.94	0.2	0.07	0.88	0.39
Shukla et al.[32]	86	CRP	0.67	0.55	0.15	0.07	0.56	0.55
Ghanem et al.[6]	109	>1, CRP	0.67 (0.45–0.84)	0.4 (0.28–0.52)	0.28 (0.17–0.42)	0.77 (0.6–0.9)		
		>2, CRP	0.29 (0.13–0.51)	0.73 (0.6–0.83)	0.27 (0.12–0.48)	0.75 (0.63–0.85)		
		△1.5, CRP	0.71 (0.53–0.89)	0.15 (0.07–0.25)	0.22 (0.14–0.33)	0.59 (0.43–0.82)		
		△2, CRP	0.63 (0.43–0.81)	0.23 (0.14–0.35)	0.22 (0.13–0.34)	0.64 (0.43–0.82)		
Virolainen et al.[33]	68		0.67	0.79				
		WBC	0.44	0.95				

PPV: positive predictive value, NPV: negative predictive value, AUC: area under curve, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: white blood cell.

Table 3. Diagnostic Value of the Synovial Marker

Study	No.	Synovial marker	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
Virolainen et al.[33]	68	Stain	0.67	1				
	68	Culture	0.75	1				
Hoell et al.[30]	115	Culture	0.05 (0.001–0.25)	0.99 (0.94–0.999)	0.5	0.83		
Williams et al.[41]	273	Culture	0.8	0.94	0.81	0.93	0.9	
Nelson et al.[37]	36	Culture	0.36	0.63				
	36	Sonication	0.82	0.5				
		Significant and intermediate	0.63	0.78				
Hoell et al.[30]	115	WBC	0.31	0.39	0.11	0.71		0.37
Kusuma et al.[31]	76	WBC	0.75	0.61	0.11	0.03	0.62	0.71
	76	%PMN	0.75	0.66	0.12	0.02	0.66	0.71
Shukla et al.[32]	86	WBC	0.78	0.96	0.7	0.03	0.94	0.91
	86	%PMN	0.78	0.82	0.35	0.03	0.81	0.81

PPV: positive predictive value, NPV: negative predictive value, AUC: area under curve, WBC: white blood cell, %PMN: percentage of polymorphonuclear cell.

Table 4. Diagnostic Value of the Tissue Marker

Study	No.	Tissue marker	Sensitivity	Specificity	PPV	NPV	Accuracy
Virolainen et al.[33]	68	Stain	0.14	1			
Della Valle et al.[42]	64	Stain	0.25	0.98	0.5	0.95	0.94
Williams et al.[41]	273	Culture	0.83	0.9	0.74	0.94	0.88
Mont et al.[40]	34	Culture	0.75	1	1	0.97	

PPV: positive predictive value, NPV: negative predictive value.

used frozen sections to confirm residual infection during two-stage reimplantation. The best current literature regarding two-stage reconstruction demonstrated that frozen section analysis only has a sensitivity of 25%, although its specificity is considerably higher[42]. Tissue culture showed a relatively higher sensitivity than other diagnostic methods (range, 0.75 to 0.83) (Table 4)[38,40]. Several studies have examined the utility of technetium/indium-labelled leukocyte imaging, gallium imaging, FDG-PET scan, and technetium Tc-99 bone marrow imaging in the primary diagnosis of PJI of both the hip and knee[33,43,44]. Given the significant variability in statistical data and methodological flaws, the American Academy of Orthopedic Surgeons (AAOS) offered a "weak" recommendation for their use in the diagnosis of PJI in select cases of equivocal laboratory investigation[45]. The MSIS criteria for the diagnosis of PJI did not incorporate nuclear imaging as a reliable method of diagnosis[3].

Outcomes

Current studies report an average high failure rate of 18% (wide range of 9%–33%) for utilizing two-stage reimplantation for the treatment of PJI[46]. The infection treatment outcomes reported for one- and two-stage reimplantation procedures are comparable, although the indications for one-stage reimplantation are more limited. One systematic review reported that the reinfection rate ranged from 0% to 41% for two-stage reimplantation and from 0% to 11% for one-stage reimplantation[47]. However, no prospective randomized clinical trials have been conducted, and most of the studies were only observational[47]. Recently, another additional systematic review and meta-analysis was conducted. The reinfection rate was 7.6% (range, 3.4% to 13.1%) in one-stage reimplantation and 8.8% (range, 7.2% to10.6%) in two-stage reimplantation. In subgroup analyses, reinfection rates remained generally similar for several study-levels and clinically relevant characteristics. Knee scores and range of motion as postoperative clinical outcomes were similar for both strategies[4]. Only a few

studies evaluated prognostic factors for successful reimplantation. Mortazavi et al.[46] evaluated predictors of failure by comparing two groups (failed and successful two-stage reimplantation). They reported that culture-negative (odds ratio [OR], 4.5 [1.3–15.7]) and methicillin resistant organisms (OR, 2.8 [0.8–10.3]) increased the risk of failure by more than four- and two-fold, respectively.

Conclusions

Although two-stage reimplantation is still the gold standard in many parts of the world, different surgical techniques are being considered since there is a considerably high failure rate. This may be due to lack of an accurate diagnostic tool for infection treatment, and there is a need for further investigation of risk factors of failure in two-stage reimplantation. The use of antibiotic-impregnated spacers are increasing, and articulating spacers may improve range of motion and increase patient satisfaction. The duration of systemic antibiotic use between stages is getting shorter, and shorter courses of antibiotic therapy have been shown to be as efficacious as prolonged therapy between the first and second stages of treatment for PJI.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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