

# Clinical Outcome of Massive Endoprostheses used for Managing Peri-prosthetic Joint Infections of the Hip and Knee

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## **ABSTRACT:**

### **BACKGROUND:**

Endoprosthetic replacement (EPR) is an option for management of massive bone loss resulting from infection around failed lower limb implants. The aim of this study was to determine the mid-term outcome of EPRs performed in the treatment of PJI and infected failed osteosyntheses around the hip and knee joint and identify factors that influence it.

### **METHODS:**

We retrospectively reviewed all hip and knee EPRs performed between 2007-2014 for the management of chronic infection following complex arthroplasty or fracture fixation. Data recorded included indication for EPR, number of previous surgeries, co-morbidities, and organism identified. Outcome measures included PJI eradication rate, complications, implant survival, mortality, and functional outcome (Oxford Hip or Knee Score; OHS/OKS).

### **RESULTS:**

Sixty-nine EPRs (29 knee and 40 hip) were performed with a mean age of 68 years (43-92). Polymicrobial growth was detected in 36% of cases, followed by coagulase-negative staphylococci (28%) and *staphylococcus aureus* (10%). Recurrence of infection occurred in 19 patients (28%); five were treated with irrigation and debridement, five with revision, one with above-knee amputation, and eight remain on long-term antibiotics. PJI eradication was achieved in 50 patients (72%); the chance of PJI eradication was greater in hips (83%) than in knees (59%) ( $p=0.038$ ). The five-year implant survivorship was 81% (95% confidence interval 74-88%). The mean OHS and OKS was 22 (4-39) and 21 (6-

43) respectively.

## **CONCLUSION:**

This study supports the use of EPRs for eradication of PJI in complex, multiply revised cases. We describe PJI eradication rate of 72% with acceptable functional outcome.

**Key words:** Peri-prosthetic joint infection, megaprosthesis, massive endoprosthetic replacement, revision arthroplasty

## **Introduction**

Peri-prosthetic joint infection (PJI) following hip and knee surgery is a potentially catastrophic complication that is associated with a significant increase in patient morbidity and mortality[1, 2]. In addition, this infection burden is likely to increase in prevalence based on the projected increase in the number of hip and knee arthroplasties and associated PJIs in the near future[3-6].

The optimum management options in PJI remain surgical; a surgical treatment algorithm exists with the following common options: Debridement Antibiotics and-Implant Retention (DAIR), implant revision (either one- or two-stage), arthrodesis, resection arthroplasty, or amputation[7, 8]. Debate remains as to the optimum treatment modality but good results (80 – 100%) have been reported with all of the above in specialized units. Despite the advances made, not all PJI is resolved with the initial surgical management and further treatment may be necessary.

Chronic, multiply revised, infected prosthetic hip and knee joints are a particular challenge for the arthroplasty surgeon. These cases pose specific difficulties due to issues relating to the poor quality of the soft tissues, the associated bone loss, biofilm formation and the need to revise the prosthesis. Following infected soft tissue debridement and excision of necrotic bone, the extent of bone-loss may be so great that the joint may not be re-constructible with revision implants. In such

extreme cases, endoprosthetic replacement (EPR) may be the only option for limb salvage. These modular megaprotheses have traditionally been used in tumour surgery with a well-documented track record of success[9-13]. The promising results have instigated the wider utilization of EPRs in treating non-neoplastic conditions such as PJIs affecting revision arthroplasties and failed osteosynthesis with significant bone loss[14-19].

The purpose of this study was to determine the mid-term clinical outcome of EPRs performed in the treatment of PJI and infected failed osteosyntheses around the hip and knee joint, and to identify factors that influence it.

## **Patients and Methods**

This Institutional Review Board approved study was a retrospective consecutive case-series of hip and knee EPRs performed between January 2007 and December 2014 for the treatment of PJI, ensuring a minimum two year follow-up period. All cases in this multi-surgeon (n=9) series were performed with a multidisciplinary team (MDT) approach in a dedicated Bone Infection Unit (BIU) consisting of experienced arthroplasty surgeons, infectious disease physicians, plastic surgeons, physiotherapists, occupational therapists, and outpatient parenteral antimicrobial therapy (OPAT) specialist nurses. In our tertiary referral center, which includes a tumour service, approximately 50 EPRs are performed annually for all indications. Two-thirds of these cases are performed for non-tumor indications, half of which are performed for PJI.

All EPRs performed for the treatment of PJI following complex arthroplasty or fracture fixation were retrieved from our institution's joint replacement database. The medical records of all the patients were reviewed for clinical and microbiological data, details of the initial prosthesis implantation and subsequent debridement surgery, antibiotic therapy along with its duration and follow-up results. Data recorded included patient demographics, indication for EPR, number of previous surgeries, microbiological organisms identified, antibiotic therapy (along with its duration), and subsequent follow-up results. Patient comorbidities were recorded using the American Society of

Anesthesiologists (ASA) score and Charlson comorbidity index score[20]. Definition of infection was based on the modified Musculoskeletal Infection Society (MSIS) criteria, which were recommended at the 2013 International Consensus Meeting (ICM) [21].

Intra-operatively, following removal of the previous implants, a comprehensive debridement and excision of infected and non-viable bone or soft tissues was carried out. Tissue sampling for microbiological and histological analysis was performed based on an established protocol that has been previously described[22]. Due to the complexity of these cases, subsequent treatment algorithms, including antibiotic protocols, were based on an individual case-by-case basis defined by the MDT. The EPR implant system used for all procedures was the Stanmore METS® (Modular Endoprosthetic Tumour System)[Stanmore Implants Worldwide, Elstree, United Kingdom]. This is a modular cemented prosthesis made of titanium alloy, which provides a range of different sized modular components in addition to a hydroxyapatite (HA)-coated collar for the bone-prosthesis junction for osseointegration (Figure 1). This prosthesis has recently been made available with the option of a silver coating in order to provide additional bactericidal properties (Agluna, Stanmore Implants Worldwide, Elstree, United Kingdom). The EPRs used in the latter part of the study had this silver coating and consisted of 9 hips and 5 knees.

Provided patients had a minimum follow-up of two years, treatment success of PJI was determined based on the ICM Delphi criteria[23]. All complications and re-operations were confirmed from medical records, postal questionnaires, and Family Practitioner records. Infection status for deceased patients was established from hospital records at the time of death. Mortality data were collected from the hospital and Family Practitioner records. Functional outcome at final follow-up was assessed using the Oxford Hip and Knee Scores (OHS and OKS) as joint specific measures in which 0 is the worst possible score and 48 the best[24].

Implant survivorship was established with revision or amputation as an endpoint[25]. For patients who had died, survival was determined by contacting

their Family Practitioner in order to determine whether or not the patient had undergone revision surgery prior to death.

### ***Statistical analysis***

Cross-tabulation, Chi-squared and Fisher's exact tests were used for categorical data. Intergroup comparisons of non-normally distributed data were made using non-parametric tests (Mann-Whitney U, Kruskal Wallis, log-rank). Survivorship was calculated with time to revision as the endpoint using Kaplan-Meier analysis with 95% confidence intervals (CI). Date of death was the date of censoring for the deceased. Statistical analysis was performed using SPSS v22 (IBM, Chicago, Illinois). A p-value  $\leq 0.05$  was considered significant.

### **Results**

A total of 69 EPR were performed during the study for the treatment of PJI (40 hips and 29 knees). There were 35 males and 34 females with a mean age at implantation of 68 years (range 43 to 92). At a mean follow up of 3.8 years (range 2 to 10), 58 patients (84%) were alive and 11 patients (16%) were deceased. Eight (12%) of the patients were lost to follow-up. The mean ASA grade was 2.5 (range 1 to 4) and mean Charlson Comorbidity Index was 1 (range 0 to 6). There was no significant difference between the hips and knees with regards to ASA grade ( $p = 0.49$ ) and Charlson Comorbidity Index ( $p = 0.521$ ). The mean number of previous surgeries prior to EPR was 3.1 (range: 1 to 10). In most cases ( $n = 45$ ; 65%), EPRs were performed for infected revision total joint arthroplasties. The indications for EPR surgery are listed in table 1.

The microbiological characteristics of the study cohort are summarized in Table 2. The type of organism isolated did not influence PJI eradication rate ( $p=0.178$ ).

The assistance of the plastic surgical team in order to perform flap coverage at the end of EPR implantation was required for 12 cases (17%). The majority of EPRs ( $n = 48$ ; 70%) were performed as a two-stage procedure whilst the remaining 21 (30%) were performed as a single-stage. This was because the patients were either too frail to undergo a two-stage procedure or because there was too much bone loss to enable secure spacer insertion. Treatment of PJI as a

single or two-stage procedure did not influence the infection eradication rate ( $p = 0.459$ )

The different complications and their management are summarized in Table 3. The overall complication rate in the study cohort was 48% with over half of the complications being accounted for by the recurrence of PJI. The complication rate (excluding PJI recurrence) was 28%. There was no significant difference in the overall complication rate between hip and knee EPRs ( $p = 0.465$ ).

PJI eradication was achieved in 50 patients (72%) (Figure 2). Subgroup analysis between hip and knee cases demonstrated that PJI eradication was more successful in the hip cohort ( $p = 0.038$ ). Infection eradication was achieved in 33 (83%) of the 40 hip cases compared to 17 (59%) of the knee cases. Albeit with the limited numbers available in this study, there was no significant difference in PJI eradication when comparing the silver-coated endoprostheses with the standard endoprostheses ( $p=0.179$ ). Of the 19 (28%) patients who had recurrence of PJI, 8 were treated with long-term suppressive antibiotics either because they were deemed unfit for further surgery or because the patient declined further surgery. The remaining 11 patients underwent surgery in the form of revision EPR ( $n = 5$ ), DAIR procedure ( $n = 5$ ), or above knee amputation ( $n = 1$ ).

There was no loss to follow up and the EPRs for 10 patients (15%) had been revised. The 5-year patient survival was 77% (CI: 63 - 91%). The overall five-year implant survivorship was 81% (95% CI: 74 to 88) (Figure 3). There was no significant difference between the survivorship of hip and knee EPRs ( $p = 0.906$ ).

The OHS and OKS questionnaires were returned by 37 (64%) of the 58 who were still alive. The mean OHS was 22 (range 4 - 39) and the mean OKS was 21 (range 6 - 43).

## Discussion

The current study provides further support for the management of chronically infected and multiply revised hip and knee PJIs within a dedicated MDT setting using megaprostheses. This is the largest case-series to date using a versatile,

modular endoprosthesis, which has traditionally been used for limb salvage in cancer surgery, to treat infected non-oncological cases. Using this management algorithm it was possible to achieve limb salvage in all but one case. More importantly, it was possible to achieve a PJI eradication rate of 72% with acceptable functional outcomes in this very complex sub-category of PJI.

Despite significant scientific advances in the field of orthopaedics over the past two decades, the diagnosis and management of PJI is arguably one of the last remaining 'frontiers' that has not yet been conquered. The gravity of this problem has been highlighted by recent publications which suggest that the five-year mortality rate of patients who suffer from PJI is greater than that of patients with certain cancers - even after adjusting for comorbidities and age[2]. In addition, studies have also documented the similarities between infectious disease and cancer at a basic science and immunologic level[26]. As such, there is now a growing view that PJIs should be treated in specialist centres within a dedicated MDT setting - much akin to the manner in which oncological cases are managed.

The outcome of PJI treatment using EPRs in this study must be interpreted in light of the complexity of the cases being treated. Approximately half of the patients in this study had undergone 3 or more previous operations on the affected joint prior to undergoing their EPR. This posed particular challenges with regards to loss of bone stock and the poor soft tissue envelope. Other salvage options for the surgical management of the chronically infected and multiply revised hip joints include amputation and resection arthroplasty[27]. Resection arthroplasty, first described by GR Girdlestone in our unit in the early 20<sup>th</sup> century, may be considered as an extreme option in refractory cases with poor bone stock[28]. However, in the modern-day arthroplasty setting, when performed in frail, elderly patients with multiple co-morbidities, the Girdlestone procedure carries a high morbidity and poor functional results[29, 30]. When all implant salvage options have been exhausted, knee arthrodesis and above knee amputation are the last remaining surgical prospects in knee PJI. Although a recent systematic review of the available evidence supports performing arthrodesis as opposed to above knee amputation (predominantly due to the

superior functional results)[31], the lack of available bone stock in many of the multiply revised cases means that knee arthrodesis is not technically possible. Indeed, this was the reason why an above knee amputation had to be performed on one of the cases in our cohort who had persistence of infection after initial EPR. Many of the patients in our study, particularly those referred in from other centers, were reluctant to consider fusion, amputation, or a Girdlestone procedure hence undergoing an EPR remained the only definitive surgical option. Eight of the 19 patients who had recurrence of PJI after their surgery were placed on long-term suppressive antibiotics either because they were deemed unfit for further surgery or they declined further surgery. The role of long-term suppressive antibiotics in resistant PJI cases and in patients unsuitable for further surgery has previously been described and we believe that it should be considered as a viable treatment option in such situations[32-34]. The proportion of 'in-operable' revision PJI patients in whom this type of management is considered is likely to increase in the future due to the projected rise in the number of revision hip and knee arthroplasties and related PJIs[3, 4].

Exploring re-infection rates is important for determining the effectiveness of any form of surgical treatment strategy used for eradication of PJI. Two systematic review and meta-analyses have recently reported on the re-infection outcomes following one- and two-stage revision total hip and knee arthroplasty (THA and TKA)[35, 36]. With regards to hips, analysis based on 98 studies showed that re-infection rates for revision THA ranged from 0 – 33% in one-stage surgery and 0 - 40% in two-stage surgery. The pooled re-infection rate for revision THA was 8.2% in one-stage surgery and 7.9% in two-stage surgery. With regards to knees, analysis based on 118 studies showed that re-infection rates for revision TKA ranged from 0 - 20% in one-stage surgery and 0 - 40% in two-stage surgery. The pooled re-infection rate for revision TKA was 7.6% in one-stage surgery and 8.8% in two-stage surgery. The overall re-infection rate of 28% (i.e PJI eradication rate of 72%) in the current study comprises 17% re-infection in the hip cohort and 41% re-infection in knees. Our PJI eradication of 83% for hip cases compares very favourably to the available literature. Subanalysis of PJI cases which were treated using proximal femoral replacements in 5



heterogenous studies demonstrates that the average PJI clearance was 78.9% (30/38) ranging from 56% to 92% [15, 16, 37-39]. In comparison to the hip EPRs, our infection eradication rate of 59% for the knees was not as favorable. This is similar to the scenario of an increased risk of PJI that is seen in primary or revision TKAs in comparison to THAs and is likely to be explained by the poor soft tissue envelope surrounding knee EPRs. This is supported by studies such as that of Mortazzavi et al. which suggest that the re-infection rate after revision TKA for infective causes was over fourfold higher than the rate of infection after revision TKA performed for non-infective causes[40]. Another recent paper, which puts the results for the knee EPR in our study into perspective, is an analysis of re-infection risk in Medicare data for 1,493,924 *primary* TKAs[41]. This study shows that, even after surgical treatment for an infected *primary* TKA, 26% of patients have a re-infection. The authors go on to predict a re-infection risk of 34.5% at 5 years. Given that this study was only analyzing primary TKAs, the high rate of re-infection demonstrates that the rate observed in our knee EPR cohort can be viewed as comparable to the existing literature. Following on from this, if the re-infection complications were excluded, the non-infection complication rate of the current study is reduced to 20%, which is very acceptable for this complex cohort of patients and comparable to previous heterogeneous studies of EPRs performed for non-tumour indications[15, 18, 38, 42-45].

With regards to the microbiological organisms isolated in the current study, the the most common finding was a polymicrobial infection which is most likely to be attributable to the large number of previous procedures which had been performed in these cases. Although the literature supports the association between some 'virulent' organisms and failure to eradicate PJI (e.g gram-negative organisms[46], enterococci[47], *Staphylococcus aureus* [48-50]), we were unable to detect this in the current study. One possible explanation for this may be the relatively small sample size causing a type II error. However, other explanations may include the aggressive treatment algorithms and strict antibiotic protocols which are applied in our unit. After accounting for the polymicrobial infections, the next two most commonly isolated pathogens were the traditional organisms isolated in most PJIs, i.e. coagulase-negative Staphylococci and *Staphylococcus aureus* [51].

Due to the small sample sizes of previous studies and the relatively high number of patients lost to follow-up, there are very few reports of implant survivorship of EPRs performed for non-tumour indications. Berend and Lombardi[17] have reported an implant survivorship of 87% at 3.8 years for distal femoral replacements, and Parvizi et al.[15] have reported an implant survivorship of 73% at 5 years. In comparison to these studies, our 5-year survivorship of 81% compares favorably, particularly when one considers that, unlike the latter two studies, all of the cases in our study were for the treatment of infection.

It is well recognized that functional outcome scores following revision surgery for infections are worse than those performed for aseptic causes[52-56]. The functional results in the current study also confirm the morbidity that can occur following chronically infected and multiply revised hip and knee joints. As a comparison, the mean OHS of EPRs performed at our own institution for non-PJI indications is 33 (compared to 22 in the current hip PJI cohort). Similarly, the mean OKS of EPRs performed at our institution for non-PJI indications is 28 (compared to 28 in the current knee PJI cohort). However, we were still able to achieve joint salvage in all but one of the cases.

This study had some limitations. Firstly, it was retrospective and hence carries with it the usual weaknesses in such studies. However, only eight (12%) of the patients were lost to follow-up, which enables us to make a meaningful interpretation of the clinical results of the study. Secondly, the average length of follow-up was not sufficient to enable us to make definitive conclusions with regards to survivorship. However, there is still adequate follow up to support the use of endoprostheses for PJI eradication in complex multiply revised cases. Thirdly, no pre-operative functional scores were available and not all patients returned the OHS/OKS questionnaires. However, the response rate of 64% achieved in this study was comparable with what is acceptable for survey response rates[57]. Finally, the sample size may not have been large enough to enable accurate sub-analysis for evaluating the effect of the microbiological organism types on the PJI eradication rate. Nevertheless, to our knowledge this remains the largest study evaluating the use of megaprostheses for the eradication of PJI in non-neoplastic cases.

370 In conclusion, this study provides further support for the use of EPRs for the  
371 management of complex hip and knee infections in tertiary centers within a MDT  
372 setting. This demonstrates that acceptable PJI eradication rates can be achieved  
373 using conventional modular megaprotheses with a proven design philosophy  
374 resulting in good survival and acceptable functional outcome.

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## Tables

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552 **Table 1: Indications for performing hip/knee endoprosthetic replacement**

553 (DAIR: Debridement Antibiotics and-Implant Retention)

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Indication	Frequency (%)
Revision hip/knee arthroplasty	45 (65)
Failed osteosynthesis	12 (17)
Failed multiple DAIRs with poor bone stock	7 (10)
Periprosthetic fracture	5 (7)

**Table 2: The prevalence of microbiological organism isolated in the 69 EPR cases**

Type of Organism	Frequency (%)
Polymicrobial	25 (36)
Coagulase negative staphylococcus	19 (28)
<i>Staphylococcus aureus</i>	7 (10)
Culture-negative	5 (7)
Other	13 (19)

**Table 3: Type of complications and their management**

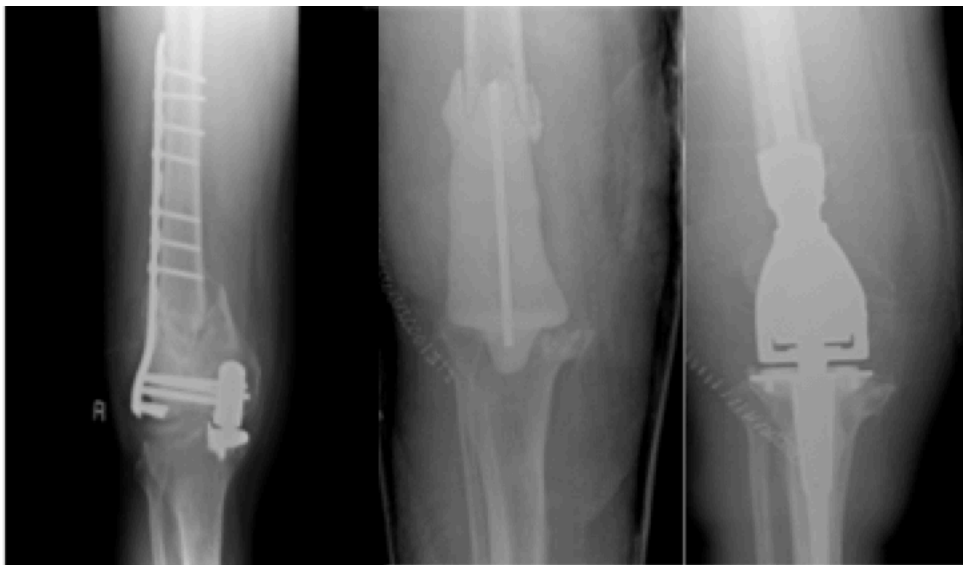
(PJI: Periprosthetic joint infection, DAIR: Debridement Antibiotics and-Implant Retention, EPR: endoprosthetic replacements)

Type of complication	Frequency (%)	Management
PJI recurrence	19 (28)	DAIR (n = 5) Revision EPR (n = 5) Above knee amputation (n = 1) Life long Antibiotics (n = 8)
Periprosthetic fracture (stem)	4 (6)	Revision EPR (n = 2)



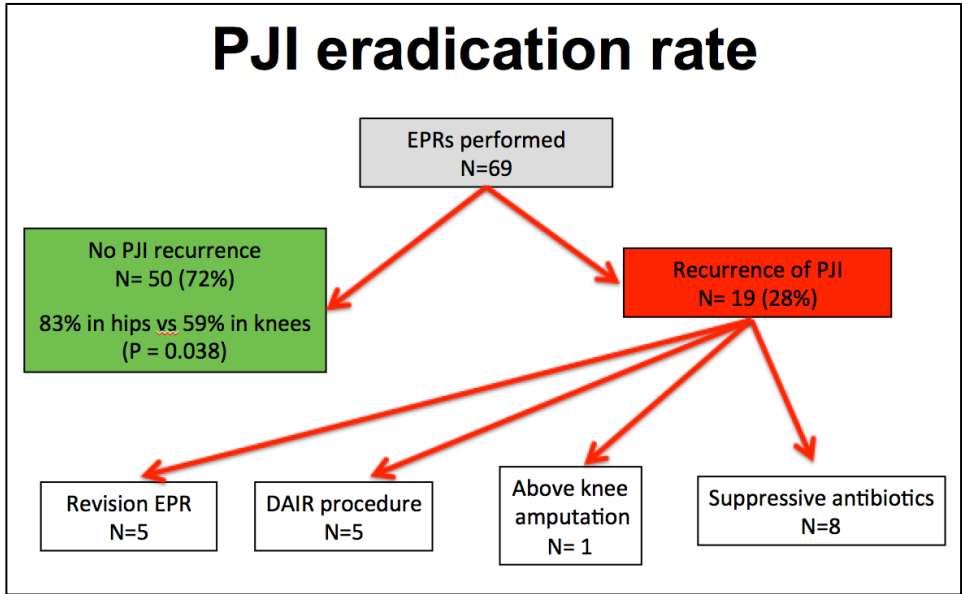
		Non-operative treatment (n = 2)
Periprosthetic fracture (acetabulum)	1 (1)	Acetabular component only revision (n = 1)
Nerve injury	3 (4)	Medical input (n = 3)
Dislocation	2 (3)	Closed reduction (n = 1) Open reduction (n = 1)
Arthrofibrosis	2 (3)	Manipulation under anaesthesia (n = 2)
Implant loosening	1 (1)	Revision EPR (n = 1)
Wound breakdown	1 (1)	Non-operative treatment (n = 1)

**Figure 1. An infected osteosynthesis around a partial knee replacement treated with two-stage implantation of an endoprosthetic replacement (EPR)**



**Figure 2. The infection eradication rate in the study cohort and the fate of patients with failure of eradication**

(EPR: endoprosthetic replacement; DAIR: Debridement Antibiotics and-Implant Retention)



**Figure 3. Kaplan Meier survival curves for hip and knee endoprosthesis replacements**

