The long-term results of a two-stage protocol for revision of an infected total knee replacement

We report the long-term results of the management of neglected chronically infected total knee replacements with a two-stage re-implantation protocol. In 18 of 34 patients (53%) a resistant organism was isolated. All cases were treated by the same surgical team in a specialist centre and had a mean follow-up of 12.1 years (10 to 14). They were evaluated clinically and radiologically using the Knee Society Score (KSS) and the American Knee Society Roentgenographic scoring system, respectively. One patient died after eight years from an unrelated cause and two were lost to follow-up. Three patients (8.8%) developed a recurrent infection for which further surgery was required. The infection was eradicated successfully in 31 patients (91.1%). There was one case of aseptic loosening after 13 years.

We found a significant improvement in the KSS at final follow-up (p < 0.001).

Infection after a total knee replacement (TKR) can be disastrous and is one of the more common causes of failure. The reported incidence of infection in modern practice is between 0.5% and 3% using contemporary infection control measures; historically, an incidence of 23% has been reported. A patient with an infected TKR may be treated with long-term antibiotics, debridement with retention of the prosthesis, arthrodesis, or by one- or two-stage re-implantation.

One-stage revision is limited to those patients who cannot tolerate multiple procedures and for those with a peri-prosthetic infection caused by a single known organism of low or negligible virulence, such as meticillin-sensitive coagulase-negative staphylococci and streptococci. It is currently used for the revision of some infected total hip replacements and gives good results in up to 80% of cases. The most successful results, however, have been reported with the use of a two-stage re-implantation protocol, which will eradicate infection in a high proportion of cases.

Over the last ten to 15 years there has been an increase in the prevalence of infections caused by resistant organisms such as MRSA and MRSE. Recent epidemiological data suggest that between 4% and 27% of all prosthesis infections are polymicrobial in origin. Most published series report on non-virulent organisms, but little information is available on the long-term results of two-stage re-implantation for the treatment of peri-prosthetic infection with resistant organisms.

The purpose of this study was to report the long-term clinical and radiological outcomes following two-stage revision in the management of a large series of TKRs chronically infected with resistant organisms.

Materials and Methods

Between January 1994 and December 1999, 34 patients with 34 chronically infected TKRs were referred to us from other hospitals and treated using a two-stage re-implantation protocol. There were 31 women and three men, with a mean age of 64 years (45 to 73). All had undergone primary surgery at other hospitals and had been referred with persistent infection. They had received antibiotics for a mean of 8.4 months (4 to 13). Data were collected prospectively. Our inclusion criteria for this study were: persistent chronic infection of a TKR, a positive culture from knee aspiration, and failure of long-term antibiotic therapy.

Data on all the patients were retrieved from the clinical records and the outpatient notes from other hospitals. Patients referred from elsewhere had a variety of symptoms, including pain, swelling, a sinus, septic necrosis of the skin and limited movement, as well as other local signs of infection.

Although the initial diagnosis was made at the referral centre, our routine diagnostic protocol, including a full blood count and measurement of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was...
We then implanted eight “burger-type” Palacos cement spacers, 13 handmade mobile Palacos spacers augmented with tobramycin and vancomycin depending on the pre-operative microbiological results and 13 commercially available preformed articulating cement spacers.

Intravenous antibiotics were then started and closely monitored by a specialist in microbiology (GD). The antibiotic regimen was determined by the organism and its sensitivities. It was administered in dosages sufficient to obtain a post-peak serum bactericidal titre (SBT) of at least 1:8. This titre reflects the level of bactericidal activity in the patient's serum at a point a quarter of the way into the interval between antibiotic doses. Blood for SBT was drawn at 1, 1.5, 2, 3 or 6 hours after the administration of the antibiotic, depending on whether the dosage frequency was every four, six, eight, 12 or 24 hours, respectively. In cases of inconsistency between intra- and pre-operative cultures, the regimen was modified according to the results of intra-operative culture and was continued for six weeks. Weight-bearing on the affected lower limb was allowed between removal of the prosthesis and re-implantation.

A second-stage procedure was undertaken when the serum levels of inflammatory markers (WBC, ESR and CRP) had remained normal for three weeks after stopping antibiotics. During re-implantation further samples were taken for microbiological and histological examination. If the intra-operative frozen section tissue was found to show > 10 neutrophil polymorphs per high-power field (hpf), we exchanged or removed the spacer and carried out a further debridement without inserting a new prosthesis.

Various revision TKR systems were used. In 19 cases we used a cemented posteriorly stabilised (PS) prosthesis (LPSflex, NexGen; Zimmer, Warsaw, Indiana), and in 15 a highly constrained condylar prosthesis (CCK) with a cementless fluted stem (Advance Revision Knee System; Wright Medical Technology Inc., Arlington, Tennessee). The transepicondylar line was used to determine the level of the joint line when introducing the femoral component. We cemented only the surface of the tibial and femoral components.

After the second procedure we followed the same post-operative protocol as for primary TKR, with three doses of intravenous vancomycin, and low-molecular-weight heparin for six weeks. Patients were mobilised on the second post-operative day, weight-bearing as tolerated. In one case we used a brace to protect the knee.

Each patient was evaluated clinically and radiologically after one, three and six months, and thereafter at one, three, five, ten and 15 years post-operatively. Clinical assessment included the Knee Society Score (KSS).19 With this scale, a score of 80 to 100 is considered excellent, 70 to 79 good, 60 to 69 fair, and < 60 poor. We compared the pre- and post-operative scores. Radiological evaluation was based on the American Knee Society Roentgenographic scoring system.20 The femoral and tibial components were divided into seven zones on the anteroposterior and lateral views, the tibial component into three zones on the lateral view. The numerical score for the components was determined by measuring the width of radiolucent lines in millimetres for each zone. For a seven-zone component, a score of < 4 is regarded as stable, a score of 5 to 9 should be monitored for possible progression, and a score of > 10 indicates loosening.

Statistical analysis. This was carried out using the paired t-test with SPSS software version 15 (SPSS Inc., Chicago, Illinois) for each criterion examined (Knee Society Score, comorbidities, re-infection, duration of antibiotic administration and bacterial antibiotic resistance). Results were considered statistically significant if p < 0.05.

Results

The mean follow-up was 12.1 years (10 to 14). One patient died eight years post-operatively from an unrelated cause with a symptom-free knee. Two patients were lost to follow-up; thus, 31 patients were available for review.

The initial indication for TKR was primary osteoarthritis in 30 patients and rheumatoid arthritis in four. A total of 21 patients (61.7%) had a prosthesis that comprised a metal femoral component and a metal-backed tibial tray, five (14.7%) had an all-polyethylene tibial tray and eight (23.5%) had a hinged prosthesis. All had undergone their primary surgery in other hospitals and presented with symptoms of infection. They had been treated with antibiotics for a variable period of time (four to 13 months) without success, 23 being treated for early post-operative infection and 11 for a late infection. Knee aspiration had been undertaken in only 19, and none had undergone any definitive treatment.
Table I. Knee Society Score (KSS) pre-operatively and at final follow-up

<table>
<thead>
<tr>
<th>KSS outcome</th>
<th>Pre-operative</th>
<th>Final follow-up</th>
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<tbody>
<tr>
<td></td>
<td>Number of cases Knee</td>
<td>Function</td>
</tr>
<tr>
<td>Excellent (80 to 100)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Good (70 to 79)</td>
<td>12</td>
<td>71 to 78</td>
</tr>
<tr>
<td>Fair (60 to 69)</td>
<td>12</td>
<td>61 to 67</td>
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<tr>
<td>Poor (&lt; 60)</td>
<td>10</td>
<td>41 to 57</td>
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<tr>
<td>Mean (SD) (range)</td>
<td>34</td>
<td>59.5 (18.5)</td>
</tr>
</tbody>
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Predisposing factors for infection were found in 21 patients (61.7%): diabetes mellitus in six cases, rheumatoid arthritis in four, chronic renal failure in four, obesity in three, urinary tract infection in two, chronic dental infection in one, immunosuppression in one, cutaneous ulceration in one and chronic anaemia in one. A significant association was detected between these comorbidities and re-infection (p = 0.04).

Pre-operative aspiration was positive for an organism in 31 knees (91.2%) and negative in the other three. After antibiotic therapy had been discontinued for at least three weeks, three knees were re-aspirated: all produced a positive culture.

All cultures were negative at the time of re-implantation. Of the organisms found at the time of the first stage Staph. aureus was the most common (14 cultures) followed by Staph. epidermidis (seven cultures) and Pseudomonas aeruginosa (four cultures).

There were no problems with wound healing and no complications affecting the extensor mechanism of the knee. The mean range of flexion six months post-operatively was 105° (95° to 120°). This remained unchanged at the time of the final follow-up. All the knees were stable.

During the first six months each patient experienced moderate pain, slight swelling, heat and redness at the site of re-operation. These symptoms progressively diminished over three to five months. Anti-inflammatory drugs helped, as did the use of ice packs and physiotherapy.

At the last follow-up the KSS score was excellent in 22 patients, good in five, fair in three and poor in one. The mean KSS improved significantly from 59.5 (41 to 78) pre-operatively to 76 (58 to 94) at final follow-up (p < 0.001). The mean functional score improved from 57 (38 to 76) pre-operatively to 74 (56 to 92) at final follow-up (p < 0.001) (Table I). The influence of comorbidities was reviewed and was not found to affect the final KSS (p = 0.114).

The mean radiological lucency scores for surviving implants were 1.5 (0 to 4) for the femoral component and 0.9 (0 to 3) for the tibial component. One case failed aseptically at 13 years after revision, with radiological lucency scores of 13 for the femoral component and 11 for the tibial component. It was revised to a highly constrained condylar prosthesis.

There were no complications in other organ systems, despite the prolonged use of powerful antibiotics, and no episodes of thromboembolic disease, despite the patients’ temporary lack of mobility (Figs 1 and 2).

Three patients (8.8%) developed a recurrent infection. These were treated using the same protocol, two successfully and one unsuccessfully. The first patient developed signs of recurrent infection eight months after re-implantation. This patient was initially treated unsuccessfully elsewhere with ten months of oral antibiotics and was then referred with loose components, which we treated using the two-stage protocol. The infecting organism was MRSA. At the second re-operation P. aeruginosa was isolated, which raised the question of whether this was recurrence or a new infection.

The second recurrence occurred four months after re-implantation. The primary organism was Staph. epidermidis. At the second-stage operation Proteus mirabilis and Staph. epidermidis were isolated.

The third recurrent infection occurred in a patient who had many contributing factors: obesity, diabetes mellitus, chronic renal failure, chronic anaemia, coronary heart disease and a long-stemmed prosthesis. She had been treated unsuccessfully elsewhere with 13 months of antibiotics. She underwent a two-stage re-implantation, with a good functional outcome. Five months later, however, she developed a new infection with a different organism (vancomycin-resistant Enterococcus). Because of her poor general condition and numerous comorbidities, an above-knee amputation was undertaken.

In six patients (17.6%) the inflammatory markers remained high despite six weeks of intravenous antibiotics. Further debridement was undertaken, new samples were obtained and a new cement spacer implanted. This was followed by a further six weeks of intravenous antibiotics. The cultures showed superinfection from a pathogen, which was not isolated. When the serum levels of all the inflammatory markers had remained normal for three weeks after stopping the second course of antibiotics, a new prosthesis was implanted.

A significant correlation was found between the duration of antibiotic administration and bacterial antibiotic resistance (p = 0.001) in each of these cases. Furthermore, these patients had undergone an empirical course of antibiotics
without aspiration of the joint and identification of the infecting organism. This was because they had been managed post-operatively by a general practitioner in small district hospitals. There was at least one comorbidity or a resistant organism present in each case.

Discussion
Over the last two decades the prevalence of infections caused by organisms such as methicillin-resistant *Staph. aureus* (MRSA) and *Staph. epidermidis* (MRSE) has increased, mainly due to the inappropriate use of antibiotics. These two Gram-positive bacteria are the most pervasive pathogenic organisms that infect TKRs; other organisms such as Gram-negative bacilli are also found, but less frequently.

Polymicrobial cultures account for 4% to 27% of all joint infections. A polymicrobial infection is said to be present when the same two or more microorganisms are isolated from at least two separate cultures of joint aspirate or intra-operative tissue specimens, or from at least one intra-operative culture of two or more microorganisms with evidence of infection in a joint space (purulence, acute inflammation, sinus tract communicating with a joint space).

In this study, all patients were referred to us after having been on long-term antibiotics. The high incidence of resistant (MRSA, MRSE or *P. aeruginosa*) organisms (18 of 34 patients, 53%) is the result of delaying operative intervention and using antibiotics empirically without having identified the infecting organism. This was obvious from the nine cases of recurrence and superinfection in which there was a significant correlation between the duration of antibiotic administration and the presence of antibiotic-resistant bacteria. We believe that prolonged empirical treatment with antibiotics in such difficult cases is inappropriate.

We treated three recurrent infections, two successfully and one unsuccessfully. It is not surprising that these patients had at least one comorbidity. An above-knee amputation was needed for one patient because of her

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**Figure 1a** – radiographs of a 68-year-old patient, showing an infected knee prosthesis with severe osteolysis. **Figure 1b** – anteroposterior (AP) radiograph immediately after introduction of an articulated antibiotic spacer. **Figure 1c and 1d** – radiographs (c) (AP, left; lateral, right) and clinical photograph (d) at two years after implantation.
grave general condition and comorbidities. The literature supports this decision in severe cases or when all other options fail.23

One remarkable aspect of our series is the excellent functional outcome that we obtained in most patients despite the presence of resistant organisms. Mittal et al16 recently reported that patients with resistant organisms (MRSA and MRSE) had a significantly higher re-infection rate (24%), either with the initial bacterial pathogen or with a different one. One polymicrobial infection was identified in our series. The patient was a 54-year-old woman with a history of diabetes mellitus who became superinfected with P. mirabilis and Staph. epidermidis.

A number of risk factors for MRSA infection have already been identified in the general hospital population.24-26 Fascia et al26 have found that older age, vascular disease, chronic obstructive pulmonary disease, open wounds and admission to a high-dependency or intensive-care unit play an important role in its pathogenesis.

The two-stage protocol is the most consistently effective method of treating an infection around a TKR.9,11,27,28 We achieved an excellent functional outcome in most of our patients, which we believe was due to the standardised approach we have described.

For how long should antibiotics be given post-operatively? In a study of 48 patients with an infected TKR managed by two-stage revision Hart and Jones29 showed that short-term parenteral antibiotic therapy in the post-operative period eradicated peri-prosthetic infection successfully in 42 of the 48 patients (88%).

Deep infection of a TKR should be confirmed by the culture of fluid aspirated from the joint under strictly aseptic conditions.18 The number of specimens suggested is at least six.17 These should be sent for culture and sensitivity testing for both aerobic and anaerobic bacteria, acid-fast bacilli and fungi. If sufficient fluid is available, complete cytological analysis and a differential white cell count are appropriate. Glucose and protein levels should also be measured, as low glucose and high protein values are compatible with infection.

Cultures of tissue obtained superficially, for example from a sinus, do not usually reflect the true identity of the microorganisms found deep in the knee joint, as fluid that drains from the knee often becomes infected on the way to the skin surface. Aspiration of the joint should only be performed once antibiotics have been discontinued. In most cases it takes one month for the cultures to become positive again after stopping antibiotics.30 Most of the cultures of aspirated fluid in our cases were positive. Synovial biopsy and culture may give more information.31

Plain radiographs of the knee cannot detect early infection; by the time radiolucent lines are present, the infection is already at an advanced stage. Technetium (Tc) and especially Ga67 bone scans or white cell scans may provide useful information.32,33 Eight patients in our series had normal radiographs and normal serum levels of inflammatory markers. A Ga67 bone scan and a white cell scan supported the diagnosis of infection in these patients, but the definitive diagnosis was only confirmed after microbiological identification of the infecting organism from the aspiration fluid and the histological examination of deep and superficial tissue specimens taken at the time of surgery.

It is well documented that a crucial step in the two-stage treatment strategy is the implantation of a cement spacer.1,2,5,13 We believe that antibiotic-loaded spacers contribute considerably to the control of infection by their local release of high doses of antibiotics.

Infection after a joint replacement is always a serious problem, and must be managed properly. The empirical administration of antibiotics without identification of the infecting organism must be avoided to minimise the risk of developing persistent organisms as well as other problems, such as bone loss and mechanical failure. Nowadays, this kind of treatment is unacceptable.
This was a prospective study of 34 patients who had a primary TKR, which became infected by a resistant organism, and who received long-term antibiotic therapy before being referred to our hospital. There are few published studies that describe such long-term follow-up. It demonstrates the importance of and high success rate associated with using a two-stage surgical protocol. Finally, for these demanding cases we advise early referral to a specialist centre with experience in the management of prosthetic joint infections.

Supplementary material

Tables detailing i) the demographic data, comorbidities, C-reactive protein (CRP) values and the duration of antibiotic administration in other hospitals of the patients included in the study, ii) the microbiological profile and the antibiotic management of the patients in the study, iii) the correlation between comorbidities and final Knee Society Score (KSS), and iv) further details of the three patients with recurrent infection are available with the electronic version of this paper on our website at www.jbjs.org.uk

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No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References