Treatment of infected retained implants

We have prospectively studied the outcome of infections associated with implants which were retained and treated using a standardised antimicrobial protocol. Over a period of four years, we studied 24 consecutive patients who had symptoms of infection for less than one year, a stable implant, no sinus tract and a known pathogen which was susceptible to recommended antimicrobial agents. The infections involved hip prostheses (14), knee prostheses (5), an internal fixation device (4), and an ankle prosthesis (1).

Twenty patients had a successful outcome at a median follow-up of 3.7 years (1.8 to 4.7); four had failure of the implant after a median follow-up of 1.2 years (0.3 to 2.5). The probability of survival without failure of treatment was 96% at one year (95% confidence interval (CI) 88 to 100), 92% at two years (95% CI 80 to 100) and 86% at three years (95% CI 72 to 100).

Patients with a short-term infection but with a stable implant, no sinus tract and a known pathogen may be successfully treated by retention of the implant and the use of a standardised regime of antimicrobial treatment.

Infection after joint replacement or internal fixation of fractures is associated with a high morbidity, increased mortality and substantial cost. The incidence of infections is likely to increase as the number of operations continues to rise and the follow-up periods lengthen. Cure of an infection associated with an implant is usually achieved by removal of the implant and associated cement, debridement of all devitalised tissue, and long-term antimicrobial treatment. Two-stage exchange arthroplasty gives the best functional results with success rates of more than 80% at a follow-up of two or more years. However, this approach may be associated with loss of bone stock, protracted immobilisation or rehabilitation, or peri-operative complications, especially in patients with significant co-morbidities. A minimally invasive surgical approach is thus an attractive form of treatment.

Several studies, in which surgical debridement and retention of the implant combined with a finite antimicrobial course were used, have reported recurrence rates of 69% to 97% after variable periods of follow-up. These studies were retrospective and the type and duration of the antimicrobial therapy were not standardised, and hence difficult to assess.

For the past decade, several investigators have reported high rates of success with surgical debridement and retention of the implant, generally exceeding 80% after a follow-up of two or more years. Only patients with stable devices and microbiologically-confirmed infections were included. In addition, antimicrobial agents with good activity against biofilm micro-organisms and excellent tissue penetration, were administered for a prolonged period of time. These findings need to be confirmed since they may have important implications for the management of infections associated with stable implants. We have, therefore, prospectively studied the outcome of microbiologically-confirmed infections associated with stable, retained implants managed by a standardised protocol of antimicrobial treatment.

Patients and Methods

The study was performed at a specialised orthopaedic hospital which serves as a referral centre for more than a million inhabitants. It has a mean of 6700 hospital admissions per year and more than 1200 joint replacements performed annually. Between January 1999 and December 2002, we prospectively included patients with an infected implant who fulfilled the following criteria: 1) duration of symptoms of infection of less than one year; 2) a stable implant on radiological and/or intra-
Definition of an infected implant. Infection was confirmed if at least one of the following criteria was present, using a previously described classification system: \(^1\) growth of the same micro-organism on two or more cultures of either a pre-operative aspirate or intra-operative tissue specimens; \(^2\) purulence of the pre-operative aspirate or intra-operative tissue, as determined by the surgeon; or \(^3\) acute inflammation on histopathological examination of intra-operative tissue sections.

According to the route of infection, it was classified as peri-operative, haematogenous, or contiguous. \(^9\) Peri-operative infections were further divided according to the presence of clinical symptoms after implantation, into those with early (within three months after surgery) or late onset (more than three months after surgery). Haematogenous infection was diagnosed if a documented or suspected bacteraemia preceded the clinical onset of infection and the original site of infection was identified. Contiguous infections referred to spread from an adjacent focus of infection.

Microbiological diagnosis. A needle aspiration of the fluid surrounding the implant was performed before surgery whenever possible. During surgery, three to five tissue specimens were collected for microbiological and one for histopathological examination. Aspirated fluid and intra-operative tissue specimens were grown on aerobic and anaerobic culture media, and incubated at 35°C for two and seven days, respectively. Isolated micro-organisms were identified using standard microbiological techniques. \(^5\) The antimicrobial susceptibility of micro-organisms was determined by the disc-diffusion method according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS). \(^7\)

Operative and medical treatment. During surgery, the implants were tested manually for stability. If the components were loose, they were removed and the patient was excluded from the study. All necrotic and fibrous tissue and bone sequestra were excised, and the surrounding region was meticulously irrigated. The wound was closed over a suction drain, which was retained for four days. If a pathogen was cultured from fluid which was aspirated before surgery, appropriate antimicrobial treatment was administered pre-operatively according to our standardised protocol. Initial antimicrobial therapy was given intravenously for two to four weeks, depending on the causative organism (Table I), followed by an oral course, in order to complete a total length of treatment of three months for a hip prosthesis or
internal fixation, or six months for a knee prosthesis. If the pathogen was not known before surgery, all antimicrobial agents were discontinued at least three days before specimens were obtained for examination. In addition, the peri-operative antimicrobial prophylaxis was deferred until after intra-operative tissue specimens had been collected, followed by empirical antimicrobial therapy (2 g of cloxacillin every six hours and 240 mg of gentamicin every 24 hours intravenously) for three to five days, and subsequently adjusted according to the type and sensitivity of the isolated pathogen.

Evaluation of outcome. All patients were observed from the date of inclusion in the study until either death, loss to follow-up, or failure of the implant. The date of entry into the study was the day of the first surgical debridement, or the first day of intravenous antimicrobial treatment, if no surgery was performed. Patients were assessed at least at one, three, six and 12 months and every six months thereafter. They were instructed to report immediately if signs or symptoms of infection appeared. At each follow-up visit, clinical signs and symptoms of infection, adherence to the protocol of antimicrobial treatment, and possible side effects of antimicrobials were recorded. In addition, laboratory blood testing which included a white blood cell count, differential count, ESR and C-reactive protein, was performed. Plain radiography of the implanted device was carried out if this was considered to be necessary and for all patients at three months after study inclusion. A successful outcome of the device was defined as a functional and pain-free implant, normal laboratory test results, and an absence of radiological signs of either loosening or pseudarthrosis. Failure of the implant was defined either as failure of treatment (clinical signs and symptoms, laboratory tests or radiological signs suggestive of recurrent infection) or failure due to other reasons (mechanical failure of the implant or re-infection with a different pathogen). Failure of treatment was further classified as confirmed (the initial microorganism was identified) or probable (no pathogen was identified). Patients with failure of an implant were observed continuously in order to determine their final status by the end of the observation period (October 1, 2004).

Statistical analysis. The probability of survival and the 95% confidence interval (CI) without failure of treatment was estimated using the Kaplan-Meier survival method. Continuous variables were compared using the Wilcoxon rank-sum test. All calculations were performed using the SAS statistical software package (Version 8.2; SAS Institute Inc, Cary, North Carolina). For graphic analysis Origin software (Version 7.5; OriginLab Corp, Northampton, Massachusetts) was used. Values for \( p < 0.05 \) were regarded as significant.

Results
We diagnosed 87 patients with infections which were related to implants. Of these, 24 (28%) met the inclusion criteria. Patients were excluded if they had a loose implant

<table>
<thead>
<tr>
<th>Table II. Characteristics of the 24 orthopaedic devices</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Type of device</td>
</tr>
<tr>
<td>Hip prosthesis (3 cemented, 3 hybrid, and 8 non-cemented)</td>
</tr>
<tr>
<td>Knee prosthesis (2 cemented, 1 hybrid and 2 non-cemented)</td>
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<tr>
<td>Internal fixation device</td>
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<tr>
<td>Ankle prosthesis</td>
</tr>
<tr>
<td>Reason for implantation</td>
</tr>
<tr>
<td>Osteoarthritis</td>
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<tr>
<td>Fracture</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Other†</td>
</tr>
<tr>
<td>Previous revisions at the site of the device</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Yes†</td>
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<tr>
<td>Type of infection</td>
</tr>
<tr>
<td>Early onset peri-operative</td>
</tr>
<tr>
<td>Late onset peri-operative</td>
</tr>
<tr>
<td>Haematogenous</td>
</tr>
<tr>
<td>Contiguous</td>
</tr>
<tr>
<td>Type of surgical intervention</td>
</tr>
<tr>
<td>Open debridement‡</td>
</tr>
<tr>
<td>No revision</td>
</tr>
<tr>
<td>Site of microbial recovery‡</td>
</tr>
<tr>
<td>Pre-operative aspirate</td>
</tr>
<tr>
<td>Intra-operative tissue</td>
</tr>
</tbody>
</table>

*pre-existing resection arthroplasty after arthritis of the hip (n = 1), pseudarthrosis of the femoral neck (n = 1), plate stabilisation after femoral elongation (n = 1), spine fixation for instability after several operations at the intervertebral disc (n = 1)
†four patients with a hip and three with a knee prosthesis
‡purulence was noted during surgery in 12 of 17 (71%) patients
§pre-operative aspirate and intra-operative tissue grew the same micro-organism in six patients (25%)
(36), an unknown pathogen (13), had violated the treatment protocol (8) or if they had experienced symptoms for more than one year (6). The median age of the 24 patients was 71 years (22 to 82); 67% were women. Infection involved predominantly hip (14) or knee prostheses (5) (Table II). In 19 patients (79%) the infection had been acquired peri-operatively with an early (11) or late clinical onset (8); four patients had a haematogenous infection identified through a distant primary focus and one had a contiguous infection with an adjacent focus of infection.

In 17 patients (71%) an open surgical debridement was performed. Seven (29%) had antimicrobial therapy only. In these patients, surgical intervention was not performed because of the extremely high risk of peri-operative complications or the patient’s refusal of surgery. No patient required more than one debridement to control their infection. Purulence of the aspirated fluid was noted in three of 13 patients (23%) and of the intra-operative tissue surrounding the device in 12 of 17 patients (71%). The median time between implantation and the first symptom of infection was 32 months (five days to nine years). The median duration of symptoms of infection before treatment was 25 days (two to 135). Patients without debridement had a significantly shorter duration of symptoms of infection (median, five days; two to 96) than those with debridement (median 27 days; five to 135; p = 0.024).

**Microbial findings.** Table III shows the distribution of pathogens. Seventeen infections (71%) were caused by staphylococci and three (13%) by streptococci. One infection was polymicrobial (Klebsiella oxytoca and Bacteroides sp.). *Staphylococcus aureus* caused early-onset peri-operative and haematogenous infections, whereas all coagulase-negative staphylococci were responsible for late-onset peri-operative infections. Resistance to methicillin was seen in 36% of *Staph. aureus* isolates and in 83% of coagulase-negative staphylococci.

**Outcome.** Of the 24 patients, one died 637 days after inclusion in the study of metastatic cancer. No other patient has been lost to follow-up. Twenty patients had a successful outcome and required no additional surgical or medical treatment during a median follow-up period of 3.7 years (1.8 to 4.7). In four, failure of the implant occurred after a median follow-up period of 1.2 years (0.3 to 2.5). Figure 1 shows the Kaplan-Meier estimate of survival without failure of treatment. The probability of survival without failure of treatment was 96% at one year (95% CI 88 to 100), 92% at two years (95% CI 80 to 100) and 86% at three years (95% CI 72 to 100).

Table IV summarises the characteristics of failures of implants. In one of the four patients (case 1), infection was diagnosed 274 days after inclusion in the study, with a different pathogen (coagulase-negative *staphylococcus*) from the original one (*Enterococcus faecalis*). This infection was...
resistant to the antibiotics administered and was therefore classified as a re-infection and not as failure of treatment. The remaining three patients had failed treatment which occurred after 123, 558 and 899 days, respectively.

In two patients (cases 2 and 3) failure was confirmed by growth of *Staph. aureus* and a coagulase-negative staphylococcus, respectively, whereas in one patient (case 4) failure was probable as no micro-organism was cultured. Both staphylococcal isolates remained susceptible to ciprofloxacin and rifampicin.

None of the seven patients with infections (four *Staph. aureus*, two coagulase-negative staphylococci, and one *Streptococcus sp.*) which had been treated with antimicrobials only, and without irrigation or debridement, had failures of treatment.

According to the patients’ reports at follow-up visits, compliance with the antimicrobial treatment regimen was over 90%. Nausea was noted in three patients who received a combination of ciprofloxacin and rifampicin, although reduction of the dose was not necessary. No other side-effects were reported.

**Final status at the end of the observation period.** Figure 2 summarises the final status of all patients at the end of the observation period (October 1, 2004). Twenty showed no evidence of failure of the implant and were free from clinical signs and symptoms of infection. In these patients, blood tests and plain radiography were normal. One patient had a re-infection with a coagulase-negative staphylococcus and required a resection arthroplasty of the hip without re-implantation. The remaining three patients who failed to respond to the treatment had confirmed (2) or probable relapse (1) of infection. Of the 24 patients, 21 were alive at the end of the observation period. One patient died from metastatic cancer during the period of this study and two died later. In one the cause was cerebral infarction and in the other it was unknown.

### Table IV. Characteristics of failures in four patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original pathogen</td>
<td><em>Enterococcus faecalis</em></td>
<td><em>Staphylococcus aureus</em></td>
<td>Coagulase-negative staphylococcus</td>
<td><em>Propionibacterium acnes</em></td>
<td></td>
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<tr>
<td>Resistant to methicillin</td>
<td>N/A*</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>No†</td>
<td>Confirmed</td>
<td>Confirmed</td>
<td>Probable</td>
<td></td>
</tr>
<tr>
<td>Involved device‡</td>
<td>Hip (H)</td>
<td>Hip (H)</td>
<td>Knee (C)</td>
<td>Hip (NC)</td>
<td></td>
</tr>
<tr>
<td>Reason for primary implantation</td>
<td>Rheumatoid arthritis</td>
<td>Pseudarthrosis</td>
<td>Osteoarthritis</td>
<td>Osteoarthritis</td>
<td></td>
</tr>
<tr>
<td>Time to device failure after study inclusion (days)</td>
<td>274</td>
<td>123</td>
<td>558</td>
<td>899</td>
<td></td>
</tr>
<tr>
<td>Duration of signs and symptoms of infection before inclusion (days)</td>
<td>125</td>
<td>8</td>
<td>100</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Age of patient at inclusion (yrs)</td>
<td>71</td>
<td>71</td>
<td>80</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Age at current review (yrs)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Purulence surrounding the device</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
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<tr>
<td>Previous revision at the site of the device</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Type of infection</td>
<td>Late onset</td>
<td>Early onset</td>
<td>Late onset</td>
<td>Late onset</td>
<td></td>
</tr>
<tr>
<td>Characteristic</td>
<td>Peri-operative</td>
<td>Peri-operative</td>
<td>Peri-operative</td>
<td>Peri-operative</td>
<td></td>
</tr>
</tbody>
</table>

* not applicable
† infection with a different micro-organism (coagulase-negative staphylococcus) than the original one
‡ H, hybrid; C, cemented; NC, non-cemented

**Discussion**

Several large studies have consistently reported low rates of success with debridement and retention of the implant, generally less than 30%.13-24 These studies were retrospective and decisions on management were made individually by the treating physicians. In particular, the antimicrobial treatment was not standardised and most reports did not specify the type and/or duration of antimicrobial therapy. Failure to use antimicrobial agents with good penetration of, and activity against, microbial biofilms for a sufficient length of time may explain the high rates of failure reported in previous series. The less effective the antimicrobial therapy, or the shorter the course of treatment, the more aggressive is the surgical approach needed for eradication of the infection, including removal of the implant.

Only a few studies showed higher rates of success with debridement and retention of the implant. These included predominantly stable prostheses, suggesting that a well-seated implant at the time of debridement is an important predictor for successful salvage of the prosthesis. In 1996, Tsukayama, Estrada and Gustilo40 reported a success rate of 68%, but debridement with retention of the implant was limited only to infections of short duration (less than one month after surgery). In 2003, Meehan et al41 reported a one-year recurrence-free rate of 89%, but only infections with penicillin-susceptible streptococci were included. These have been shown to be associated with a better outcome when compared with infections from other organisms, probably reflecting their lower virulence.14,20,21 In our study, we included infections with all types of micro-organism and those with longer duration (up to one year) as long as the implant was stable. The rate of success was 96% after one year, 92% after two years and 86% after three years.

Our results are consistent with those of previous reports using this approach.25-29 Several characteristics are com-
mon in these studies. First, the patient population was carefully selected, including only individuals with a stable implant, no sinus tract and a known pathogen. Secondly, surgical debridement was performed as early as possible during the course of the infection. Thirdly, a standardised protocol of antimicrobial treatment was used, including the combination of a quinolone and rifampicin for staphylococcal infections. After initial intravenous treatment, oral agents with good bio-availability and tolerability were administered for three to six months depending on the type of device, thus enabling the eradication of infection rather than the suppression of clinical symptoms.

The role of rifampicin in staphylococcal infection is not controversial.\textsuperscript{38} The micro-environment around the implant supports the formation of a biofilm, which makes the eradication of infection difficult.\textsuperscript{42} Rifampicin has shown bactericidal activity against staphylococcal biofilms \textit{in vitro}, in experimental animal models, and in clinical studies.\textsuperscript{25,26,43-49} Biofilm microorganisms have dramatically increased resistance to antimicrobial agents, as compared with their free-living counterparts, probably reflecting their reduced growth rate.\textsuperscript{50} Thus, treatment with antimicrobial agents which are active against surface-adhering, slow-growing micro-organisms is crucial for the eradication of infections associated with biofilms.\textsuperscript{43,46} Since resistance against rifampicin can develop rapidly in staphylococci, a combination with an additional agent was used (Table I).

In our study, the median duration of symptoms before the initiation of treatment was longer (25 days) than that suggested by several investigators for successful salvage of the prosthesis (less than 14 days).\textsuperscript{15,21,41} In acute infections, such as those caused by \textit{Staph. aureus}, early intervention plays a critical role. In low-grade infections however, caused by coagulase-negative staphylococci, a well-fixed implant, the absence of a sinus tract and antimicrobial susceptibility of the pathogen appear to be more important.\textsuperscript{13,51} According to our study protocol, patients having no surgical debridement were also included in order to compare their outcome with those for whom an early surgical debridement had been performed. Surprisingly, none of the seven patients who received antimicrobial therapy alone failed to respond to treatment. This favourable outcome may be attributed to the lack of sinus tract, shorter

\* One patient died 637 days after inclusion in the study because of an unrelated cause.
\† Persistent pain at the site of total hip replacement. No micro-organism was detected in repeated fluid aspirates. The patient did not receive antimicrobial treatment and no radiological loosening of the prosthesis was observed. At the last follow-up ten months after occurrence of pain, all laboratory blood test results were normal and the prosthesis was stable on radiological examination.
\‡ Infection with methicillin-resistant \textit{Staphylococcus aureus}. Treatment with vancomycin and rifampicin, successful outcome four months after second revision. The patient died of cerebral infarction three months after completing antimicrobial therapy.
\§ Infection with coagulase-negative \textit{staphylococcus}. Successful control with long-term oral antimicrobial suppression with minocycline (100 mg once daily orally).

Fig. 2

Final status of the 24 infections, which had been initially treated by retention of the implant, at the end of the observation period.
duration of symptoms of infection (median, five days vs 27 days), and early initiation of antimicrobial therapy. Nevertheless, this finding is intriguing since antimicrobial therapy without concomitant surgical intervention is not considered to be standard treatment. Without debridement, suppression of symptoms is usually achieved rather than eradication of the infection.9

Our study has several limitations. First, as a result of narrow inclusion criteria, our sample is small but was conducted prospectively, according to the status of the implant (stable implant), surrounding soft tissue (no sinus tract), microbiology (known pathogen), and antimicrobial treatment (type and duration). Secondly, we included a heterogeneous group of implants which usually demand an individualised surgical approach. However, the principles of microbial biofilms such as increased antimicrobial resistance, production of extracellular matrix and persistence of infection, apply universally to all types of foreign body. Therefore, we focused on factors which were important to the eradication of infections associated with biofilms such as stability, causative micro-organism, and antimicrobial treatment. Thirdly, given the small number of patients who failed to respond, we were not able to identify risk factors for failure. Some relapses of infection may not present clinically for several years. Therefore, a follow-up period of more than five years may provide additional data on the outcome of long-term treatment. Both patients who failed treatment had a relapse of infection with a methicillin-resistant Staphylococcus suggesting that this may be associated with failure of treatment in staphylococcal infection, as has been suggested by other investigators.21,52

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

References


