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Outcome of prosthetic knee-associated infection: evaluation of 40 consecutive episodes at a single centre

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ABSTRACT

Few studies have compared the long-term success of different surgical strategies in prosthetic knee-associated infection. Accordingly, a retrospective cohort study was performed of 40 episodes in 35 consecutive patients undergoing revision surgery for prosthetic knee-associated infection at a single centre between 1988 and 2003. The median patient age was 70 (44–90) years; the median follow-up period was 28 (2–193) months; 45% of infections were early, 23% were delayed, and 32% were late; and 55% of infections were caused by staphylococci. The probability of survival without prosthesis failure was 92.4% (95% CI, 84.1–100) after 1 year, and 88.7% (95% CI, 78–99.4) after 2 years. Recurrence-free survival was observed in 20 (95%) of 21 patients treated with debridement and retention, in both patients with one-stage exchange, and in 11 (85%) of 13 patients with two-stage exchange. Patients with delayed infection had a worse outcome than those with early or late infection (67% vs. 97%; $p < 0.03$). Patients with at least partially adequate antimicrobial therapy had a higher success rate than those with inadequate treatment (94% vs. 60%; p 0.069). The outcome was similar for patients with a duration of therapy of 3 to <6 months, and those with a duration of therapy of ≥6 months (91% vs. 87% success). Different surgical procedures had similar success rates, provided that the type of infection, the pathogen, the stability of the implant and the local skin and soft-tissue condition were considered. Adherence to an algorithm defining a rational surgical and antibiotic treatment strategy contributed to a favourable outcome.

Keywords Arthroplasty-associated infection, debridement, knee infection, rifampicin, surgical procedures, therapy

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INTRODUCTION

Infection associated with total knee arthroplasty (TKA) occurs in 0.5–2% of patients during the first 2 years following primary knee replacement [1–4]. Treatment of such infections costs three-to-four times more than the primary arthroplasty itself [5]. Treatment options can be classified into prosthesis retention, prosthesis exchange and salvage procedures (arthrodesis or amputation). The goal of therapy is eradication of infection, resulting in a pain-free, functional joint. Antimicrobial suppression, arthrodesis or amputation fulfil these requirements only partly. In contrast, debridement with retention (combined with appropriate antimicrobial therapy), one-stage exchange and two-stage exchange are the three procedures which have the potential to achieve the above goal [1,2]. Since controlled trials comparing these different surgical options are lacking, and will probably never be performed, the choice of the optimal treatment is still a matter of debate.

The morbidity and mortality associated with repetitive surgery and anaesthesia are considerable. In addition, repetitive invasive procedures may cause bone, muscle, soft-tissue and skin defects, resulting frequently in impaired functional integrity. Thus, the least invasive procedure resulting in cure of infection is preferable. However, not only medical but also legal aspects may play a role in choosing a specific surgical

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technique. Until now, the selection of surgical intervention was driven mainly by the tradition at individual institutions, and was not based on well-defined criteria. However, such criteria have been published recently [2,6,7]. In many centres, two-stage exchange is considered to be the procedure with the best chance of curing infection [8–16]. Nevertheless, this procedure is costly, time-consuming, and may result in increased damage to bone, soft-tissue and skin. However, based on case series and a single controlled study, the intervention should be chosen according to the type of infection (early, delayed or late), the duration of infection, the stability of the implant, the type of microorganism causing infection, and the quality of the soft-tissue [17–19]. In patients with prosthetic hip-associated infection, the outcome was best if the patients were treated according to a well-defined algorithm [7]. In the present retrospective cohort study, the characteristics and outcome of TKA-associated infections treated with different types of surgical and antimicrobial approaches were evaluated.

PATIENTS AND METHODS

Setting, study site and patients

A retrospective cohort study was conducted of 40 consecutive episodes in 35 patients undergoing surgery for TKA-associated infection between November 1988 and December 2003. The Clinic of Orthopaedic Surgery is a 48-bed unit, serving as a primary-care centre for orthopaedic surgery of the extremities, and as a tertiary-care centre for revision arthroplasty. During the 15-year study period, 534 patients with primary knee arthroplasty were identified, among whom 13 (2.4%) developed TKA-associated infection. In addition, 22 patients were referred with TKA-associated infection from other hospitals. All 35 patients (40 episodes) were followed prospectively at regular intervals. Data extracted from medical charts and electronic files included: orthopaedic case history, type of infection, signs and symptoms of infection, laboratory parameters of infection, microbiology and histopathology results, imaging procedures, and surgical and antimicrobial therapy.

Definition of infection

TKA-associated infection was diagnosed if a sinus tract communicating with the joint space was present (documented by arthrography or during surgery), or if at least two of the following criteria were present: (1) at least one positive intraoperative tissue or synovial fluid culture; (2) ≥ 5 neutrophils per high-power field in peri-prosthetic tissue specimens; (3) >1700 leukocytes/μL and/or $>65\%$ neutrophils in synovial fluid [20]; (4) clinical and laboratory signs of infection; or (5) radiological signs of infection. According to the time-interval between implantation and clinical onset of infection, infections were categorised into early (≤ 3 months after surgery), delayed (>3–24 months after surgery) and late (≥ 24 months after surgery) infection.

Outcome evaluation

'Cure' was defined as an absence of clinical signs and symptoms of infection, a C-reactive protein level of <10 mg/L or an erythrocyte sedimentation rate of <20 mm/h, and the absence of radiological signs of infection at a follow-up visit ≥ 2 years after beginning antimicrobial treatment. In the case of a second episode caused by haematogenous seeding or by a new exogenous infection, cure of the first episode was defined as the absence of the original microorganism during revision for the second episode. 'Probable cure' was defined by the same criteria as above, but with a follow-up period of <2 years. A 'new infection' was diagnosed if a new pathogen was identified after initial cure, or if the infection involved a knee prosthesis on the other side. 'Definite failure' was defined as persistence or recurrence of TKA-associated infection with the same or an unknown pathogen during or after the completion of antimicrobial therapy. 'Probable failure' was a possible persistence or recurrence of TKA-associated infection that did not fulfil the strict criteria for a TKA-associated infection. 'Early death' was defined as death within 28 days of the most recent surgical intervention. 'Death caused by sepsis' was defined as death related to uncontrolled TKA-associated infection.

Appropriateness of treatment

The first surgical intervention performed for each episode was compared to a treatment algorithm published previously [2,6,7] and was categorised as: (1) treatment according to the algorithm, or more invasive therapy (e.g., two-stage instead of one-stage exchange); or (2) less invasive therapy (e.g., retention instead of prosthesis exchange). Similarly, antimicrobial treatment was evaluated in comparison with published guidelines [2] and classified as: (1) adequate therapy, defined as an antimicrobial agent given for a total duration of ≥ 6 months with initial intravenous administration for ≥ 2 weeks (≥ 6 weeks in patients undergoing two-stage exchange with an 8-week interval if culture-negative at reimplantation), use of appropriate drugs according to antimicrobial susceptibilities and published clinical studies, use of drugs with efficacy against surface-adhering bacteria whenever possible [21–25] and with good bioavailability; (2) partially adequate therapy, defined as use of an appropriate drug for 3 to <6 months or initial intravenous administration for ≤ 2 weeks; or (3) inadequate therapy, defined as antimicrobial therapy that did not correspond to either of the above categories.

Statistical analysis

For outcome analysis, categories were defined as 'success' (cure or probable cure of the original infection) or 'failure' (definite or probable persistence or recurrence, early death resulting from any cause, or death resulting from sepsis). Categorical data were evaluated using a two-sided Fisher's exact test. The probability of survival and 95% CI without failure were estimated using the Kaplan–Meier survival method. If a new infection involved the prosthesis, the

preceding episode was censored. Calculations were performed using JMP v.5.1.2 (SAS Institute, Cary, NC, USA), with Origin v.7.5 (OriginLab Corp., Northampton, MA, USA) used for graphical analysis.

RESULTS

Demographic data

Table 1 summarises the characteristics of 40 episodes of TKA-associated infection in 35 patients. No previous revision had been performed in 18 (45%) episodes; one revision preceded infection in 12 (30%) episodes; and at least two revisions preceded infection in ten (25%) episodes. Risk-factors for prosthetic joint-associated infection were diabetes mellitus (seven cases, 20%) and rheumatoid arthritis (six cases, 17.1%). One patient had simultaneous haematogenous seeding in both prosthetic knees during sepsis caused by *Staphylococcus aureus*. Four of the remaining 34 patients had a second episode of TKA-associated infection involving the same prosthesis. In one episode, the infection was considered to be a recurrence; the other three episodes were new infections. In one case, the second episode occurred after arthrocentesis for a haemarthros following knee distortion. In another case, the second infection occurred after a penetrating injury of the pre-patellar bursa by a plant thorn, causing a *S. aureus* soft-tissue infection. The third re-infection was caused by haematogenous seeding during sepsis.

Clinical characteristics

Eighteen episodes were early infections (median 35, range 2–92 days). These infections were acquired by the exogenous route, since no other infectious focus with the same pathogen was detected. Delayed infections were found in nine episodes after a median of 311 days (range 113–558 days). Thirteen episodes were late infections, acquired predominantly via the haematogenous route and manifesting after a median of 2908 days (range 778–7777 days). Overall, in 16 (40%) episodes the clinical manifestation was acute, characterised by a systemic inflammatory response syndrome, including fever of >38°C in eight (20%) episodes. Moderate pain (regular need for analgesics during locomotion) or severe pain (present at rest) was observed in 25 (62.5%) episodes, local inflammation in 27 (67.5%) episodes, and sinus tract, abscess or wound dehiscence in ten (25%) episodes.

Table 1. Characteristics of 40 episodes of total knee arthroplasty infection

Characteristics	
Demographics	
Median age (range), years	70.1 (43.5–90.1)
Male, *n* (%)	17 (48.6)
Median follow-up (range), months	28 (2–193)
Infection	
First infection, *n* (%)	36 (90.0)
Re-infection, *n* (%)	4 (10.0)
Type of infection	
Early (≤ 3 months), *n* (%)	18 (45)
Delayed (> 3–24 months), *n* (%)	9 (22.5)
Late (> 24 months), *n* (%)	13 (32.5)
Type of acquisition of infection	
Exogenous, *n* (%)	25 (62.5)
Haematogenous, *n* (%)	15 (37.5)

Microbiology

Table 2 summarises the spectrum of causative microorganisms which were identified in 95% of episodes. Two episodes comprised mixed infections, and no microorganism was cultured from two episodes. Pathogens were identified by intraoperative cultures (median, four positive tissue specimens) in 27 (67.5%) episodes, and by synovial culture in ten (25%) episodes. One episode (caused by *S. aureus*) was documented microbiologically only by a deep sinus tract culture.

Surgical and antimicrobial treatment

In 21 (52.5%) episodes, the prosthetic joint was retained, and 20 patients had symptoms for <3 weeks. In ten cases, revision surgery, i.e., synovectomy, control of stability of the implant,

Table 2. Pathogens isolated from cases of total knee arthroplasty infection

Microorganism[a]	No. (%)
Staphylococcus aureus[b]	14 (33.3)
Coagulase-negative staphylococci[c]	9 (21.4)
Streptococcus spp.	5 (11.9)
Escherichia coli	3 (7.1)
Pseudomonas aeruginosa	2 (4.8)
Enterococcus faecalis	3 (7.1)
Peptostreptococcus spp.	1 (2.4)
Propionibacterium acnes	1 (2.4)
Hafnia alvei	1 (2.4)
Granulicatella adiacens	1 (2.4)
No growth	2 (4.8)

[a]Two episodes were mixed infections, one with *S. aureus* plus *Ent. faecalis*, and one with *S. aureus* plus coagulase-negative staphylococci.
[b]None of the *S. aureus* isolates were methicillin-resistant.
[c]Five (55.6%) of nine isolates of coagulase-negative staphylococci were methicillin-resistant.

debridement and suction drainage, was performed. Seven episodes were treated surgically by arthroscopic lavage. In four episodes, early postoperative superficial wound debridement was performed without re-opening the joint. One-stage exchange was chosen in only two (5%) episodes. In 13 (32.5%) episodes, two-stage exchange was the initial treatment option. In each case of exchange arthroplasty, debridement and suction drainage was performed. A spacer was placed in five cases, and external fixation was used to bridge the knee in eight cases. The median interval from device removal to reimplantation was 35 days (range 13–116 days). Finally, three episodes were treated with arthrodesis, and in one episode amputation was required because of uncontrolled sepsis.

Table 3 summarises the details of the antimicrobial therapy administered. Adequate, or partially adequate, antimicrobial therapy was administered in 35 (87.5%) episodes. Until 2002, patients with quinolone- and rifampicin-susceptible staphylococcal TKA-associated infection were treated with ciprofloxacin plus rifampicin. Thereafter, such patients were prescribed levofloxacin plus rifampicin, following initial intravenous treatment with flucloxacillin or vancomycin plus rifampicin.

Outcome

The median duration of follow-up after the first surgical intervention was 28 months (range 2–193 months). Fig. 1 shows the Kaplan–Meier estimate of survival without failure. The probability of survival without failure was 92.4% (95% CI, 84.1–100) after 1 year, and 88.7% (95% CI, 78–99.4) after 2 years. Thirty-six of 40 episodes had a successful outcome and required no additional surgical or medical treatment during a median follow-up period of 877 days (range 236–5879 days). Three failures occurred during the first year and one during the second year (at day 624). In 27 (67.5%) episodes followed for ≥2 years, there was a success rate of 92.6% (25 of 27 episodes). Probable success, i.e., no signs of infection, was observed during a follow-up period of <24 months in three patients who died, in six patients who were included during the year 2003, and in one patient who was lost to follow-up. Seven (20%) of 35 patients died during the follow-up period.

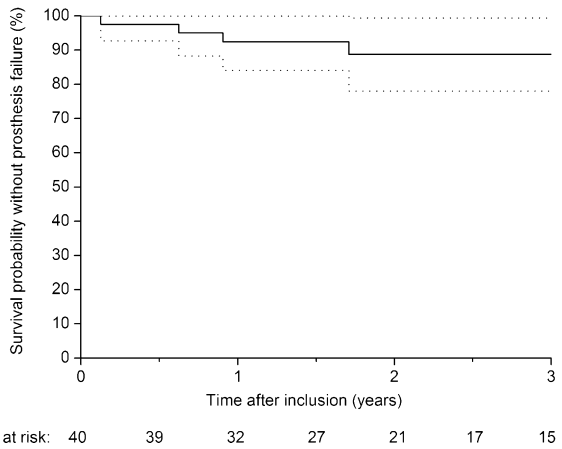

Fig. 1. Kaplan–Meier estimate of survival without failure in 40 episodes of total knee arthroplasty-associated infection. The median follow-up in patients without failure was 838 days (range 236–5879 days).

Among the four episodes in patients with treatment failure, three had a persistent infection with the same pathogen. One patient died from sepsis despite upper leg amputation, and another received ciprofloxacin plus a placebo for *S. aureus* infection, according to a treatment protocol of a double-blind study published previously [17]. One patient acquired a new exogenous infection during revision; this infection persisted despite a further two-stage exchange of the prosthesis. The two patients with delayed TKA-associated infection had clinical symptoms for a duration of >4 weeks. Table 3 shows the outcome according to antimicrobial therapy. Those patients with a treatment regimen that was at least partially adequate had a cure rate of 94.3%, compared with a rate of 60% (p 0.069) for the other patients.

Table 4 summarises the success rates according to adherence to the algorithm, to type of infection,

Table 3. Outcome according to antimicrobial therapy

According to	Success rate, no. (%)
Appropriateness of antimicrobial treatment[a]	
Adequate	26/28 (92.9)
Partially adequate	7/7 (100.0)
Inadequate	3/5 (60.0)[b]
Type of long-term oral treatment	
Quinolone (ciprofloxacin or levofloxacin)[c]	18/20 (90.0)
β-Lactam	7/7 (100.0)
Other[d]	5/6 (83.3)
No long-term oral treatment	6/7 (85.7)
Combination therapy including rifampicin	22/23 (95.7)
Duration of antimicrobial therapy[e]	
Total treatment ≥6 months	20/23 (87.0)
Total treatment <6 months	10/11 (90.9)

[a]For definitions, see Patients and methods.
[b]Adequate/partially adequate vs. inadequate: p 0.069.
[c]Mostly in combination with rifampicin.
[d]Fusidic acid, clindamycin, linezolid.
[e]Six episodes in patients with two-stage exchange without spacer were excluded (see Patients and methods).

Table 4. Outcome according to surgical therapy

Variable	Success rate, no. (%)
Algorithm	
Yes	24/26 (92.3)
No	12/14 (85.7)
Infection type	
Early	18/18 (100.0)
Delayed	6/9 (66.7)[a]
Late	12/13 (92.3)
Pathogenesis	
Haematogenous	15/15 (100.0)
Exogenous	21/25 (84.0)
Type of surgery	
Debridement and retention	20/21 (95.2)
One-stage exchange	2/2
Two-stage exchange	11/13 (84.6)
Arthrodesis	3/3
Amputation[b]	0/1

[a]Fisher's exact test: $p < 0.03$ vs. early/late infection.
[b]Early death caused by co-morbidity.

to pathogenesis, and to the different surgical techniques used. The outcome did not differ significantly for patients treated according to the algorithm, or for patients with different types of pathogenesis (exogenous, haematogenous) or surgery. In contrast, the success rate was significantly lower for patients with delayed infection than for those with early or late infection (66.7% vs. 96.8%; $p < 0.03$). Retention had an overall success rate of 95.2%, with a rate of 100% if the retention was treated surgically with synovectomy (ten episodes), or 90.9% with arthroscopic lavage. The only patient with treatment failure received inadequate long-term oral antimicrobial treatment, namely ciprofloxacin alone against *S. aureus* (see above).

The median follow-up period for six cases treated with levofloxacin plus rifampicin was 22 months (range 20–28 months). At the latest follow-up visit, these patients had a probable success rate of 100%. Five of these patients were treated with debridement and retention, and one patient was treated with two-stage exchange of the prosthetic joint.

Functional result

After treatment, 52.8% of patients were mobile without a crutch, 19.4% required one crutch, 13.9% required two crutches, and 8.3% needed a wheelchair. One patient was not mobilised, and information regarding the mobility of another patient was missing. Three of the patients needed an aid (crutch or wheelchair) for reasons other than the functional result of the TKA, namely Parkinson's disease, amputation of the contralateral leg following a traffic accident, and cerebrovascular ischaemia.

DISCUSSION

The main finding from this study was the observation of a similar outcome for TKA-associated infection following the application of different surgical strategies defined in a treatment algorithm. Success rates after two-stage exchange, one-stage exchange or debridement with retention were 85%, 100% (2/2) and 95%, respectively. Results from case series and cohort studies are the only resource for defining the rational and optimal treatment strategies for different types of infection [2]. In the centre described in the present study, all patients were followed prospectively at regular intervals, and data were saved on electronic files [26].

Traditionally, two-stage exchange, combined with treatment with intravenous antibiotics for 6 weeks, is the preferred regimen, especially in the USA [8]. With this technique, the chance of survival without recurrence is 89–100% [9,11–16,27,28]. Retention with life-long antibiotic suppression is an alternative for patients with whom extensive surgery is considered to be too great a risk [2]. Since the goal of treatment is the elimination of infection while conserving the functional integrity of the joint, the latter option is not suitable, as it does not fulfil both requirements. Therefore, the outcomes associated with a differential approach to different surgical strategies, namely debridement with retention, one-stage exchange and two-stage exchange, were evaluated. These procedures were not chosen at random, but according to criteria published previously [2,6,7]. The overall success rate of relapse-free survival was 90% with a median follow-up of 28 months, and 92.6% if only patients with follow-up for >2 years were analysed. The microorganisms causing infection were comparable to those reported in other studies, namely one-third *S. aureus*, one-fifth coagulase-negative staphylococci, and 12.5% streptococci [1,29].

One-stage exchange is performed rarely in patients with TKA-associated infection. In the present study, it was used in only two (5%) of the episodes, and both cases had a favourable outcome. This approach was used rarely because most patients with prolonged symptoms had a poor skin and soft-tissue quality; however a

German study reported a success rate of 73% (76/104) with a follow-up of 5–15 years [30]. In a Swedish study, 75.5% (81/107) of patients with infected TKA were treated successfully, with no difference between patients with one-stage or two-stage procedures [3].

In contrast to most other studies, half of the patients (21/40 episodes) in the present study were treated with debridement and retention. This procedure has been reported to have a high failure rate with prosthetic joint infection, ranging from 40% to 83% in nine studies of patients with TKA-associated infections [4,31–38]. Few studies have reported a better outcome, but Mont *et al*. [39] reported a failure rate of only 17% in 24 patients with post-operative or late haematogenous infections. In the present study, the type of infection had a crucial effect on the outcome. Whereas the success rate was only 66.7% in patients with delayed infection, it was 100% (18/18) in patients with early infection, and 92.3% (12/13) in patients with late haematogenous infection. Thus, as reported previously, the short duration of infection in patients with early and haematogenous infections is a prerequisite for a favourable outcome if the device is not replaced [17,31].

Patients who received surgical treatment according to a published algorithm had a slightly better outcome than other patients (92.3% vs. 85.7%), although this difference did not reach statistical significance, probably because of the small sample size. However, it is possible that the choice of the surgical procedure is less important in TKA than in hip prosthesis-associated infection, where a previous study found that the difference was statistically significant [7].

The type of antimicrobial therapy, and probably also the duration, plays an important role in patients with device retention. Long-term therapy with a rifampicin-containing combination in patients with staphylococcal orthopaedic implant-associated infection was 100% successful in a controlled study, and was 86% successful in a recent observational study [17,19]; however, only a minority of patients in these studies had knee prostheses. Rifampicin has a special efficacy on biofilm-associated and stationary-phase staphylococci [21–25]. In the present study, 23 patients treated with rifampicin-containing combinations had a success rate of 95.7%, confirming the good results in previous studies with a larger series of patients with total knee arthroplasty.

The duration of therapy has not been tested in comparative studies, and is therefore still a matter for debate [1,28]. In the present study, patients who received therapy for 3 to <6 months had an outcome similar to that of patients who received therapy for ≥ 6 months. Several previous studies of patients with implant retention have advocated use of antibiotics for several months [17–19], and in view of the good results obtained in these, but not in other studies [4,32–36], a treatment duration of ≥ 3 months seems rational. In a recent study, the failure rate in 35 patients with two-stage exchange and a 6-week course of antibiotics was 14% [40]. In contrast, in three of 34 patients with persistently positive cultures after therapy for 6 weeks, there were no treatment failures after therapy for an additional 6 weeks. Thus, even in patients with two-stage exchange, antimicrobial therapy for ≥ 3 months is advisable if cultures are positive or were not performed at the time of reimplantation.

In conclusion, debridement with retention of the knee arthroplasty had a similar outcome to two-stage exchange in patients with early and late haematogenous infections with a short duration of symptoms (< 3 weeks), a stable implant, reasonable skin and soft-tissue quality, and long-term antimicrobial therapy.

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