

A Treatment Pathway Variation for Chronic Prosthesis-Associated Infections

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Background: Periprosthetic joint infections (PJIs) are relatively rare but are on the rise because of the increasing total number of implantations performed. Treatment of PJI remains individualized and involves both surgical and medical treatment, with variations depending on the time of implantation, the duration and severity of the infection, tissue damage, and the underlying microorganism. In this case series study, we investigated clinical and functional outcomes of a variation of the Liestal algorithm in patients with PJI following total hip arthroplasty.

Methods: This study included 32 patients (33 cases) who were treated for chronic PJI with 2-stage exchange using a cement spacer during the period of 2003 to 2014. In contrast to other treatment pathways, antibiotic therapy was targeted to the causative microorganism as early as possible despite the presence of a cement spacer. Second-look surgery was performed 4 days after removal of the primary implant and a 4-week antibiotic-free window was interposed before definitive reimplantation. Thereafter, antibiotic treatment continued for approximately 6 weeks. All patients were followed for a minimum of 2 years. Parameters investigated were the duration of infection-free survival, functional outcome, and epidemiological data.

Results: At 2 years of follow-up and at the most recent follow-up (on average, 7 years after reimplantation), 100% of the patients were free of signs of infection, and the mean Harris hip score (HHS) was 89 at the latest follow-up.

Conclusions: A meticulously performed 2-stage exchange for PJI with early targeted antibiotic treatment, second-look surgery, an antibiotic-free window before reimplantation, and antibiotic treatment post-reimplantation of medium duration is associated with excellent infection-related and good functional outcome after ≥ 2 years of follow-up even in cases of chronic PJI.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Periprosthetic joint infections (PJIs) are relatively rare, with a global incidence of around 1% to 2% in the first 2 years after primary hip arthroplasty. Such infections are, however, on the rise because of the increasing total number of implantations performed, and they are a major cause of implant failure and revision surgery, with substantial medical and socioeconomic impact^{1,5}.

Various treatment strategies exist. Zimmerli et al. developed the well-established Liestal algorithm, with combined surgical and antibiotic therapies^{6,7}. Other studies have highlighted global trends in the management of PJI. In North America, 2-stage exchange is the gold standard⁸, and an antibiotic-free window between stages is more frequently implemented there than in Europe⁹.

In a systematic review and meta-analysis of studies with different strategies but a minimum of 2 years of follow-up, Kunutsor et al. found a pooled reinfection rate of approximately 8% (range, 0% to 40%) after 2-stage revision¹⁰. The Liestal algorithm, which is often used in Europe for the treatment of PJI, recommends 2-stage exchange primarily for long-lasting infections with damaged soft tissue and/or a sinus tract⁶. Several studies have analyzed its effectiveness. Giulieri et al. showed (with a 90% success rate) that the Liestal algorithm could be applied to the treatment of PJI in clinical practice¹¹. In 2011, De Man et al. confirmed the excellent infection-related results but reported an inferior functional outcome following 2-stage compared with 1-stage revision¹². Five years later, Born et al. again corroborated the high success rate of the Liestal algorithm¹³.

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TABLE I Comparison of the Liestal Algorithm⁷ and Our Treatment Variation for 2-Stage Exchange Due to Periprosthetic Joint Infection (PJI) Following Total Hip Arthroplasty*

2-Stage Exchange	Liestal Algorithm	Our Treatment Variation
Included clinical manifestations	According to the time of onset (delayed or late)	According to the duration of infection (chronic infections)
Possible soft-tissue conditions	Sinus tract, abscess	Sinus tract, abscess, failed previous surgery
Microorganisms	No restrictions	No restrictions
Suction/irrigation	3 days	No
Second-look surgery after explantation surgery	If fluid accumulation	Yes
Provisional solution	Spacer or extension (according to pathogen)	Spacer, never extension
Duration of antibiotic therapy before reimplantation	2-4 (IV) or 6-8 wk (IV and oral) according to pathogen characteristics	8 wk
Antibiotic free window before reimplantation	2-4 days	4 wk
Use of biofilm-active antibiotics with spacer in situ	No	Yes
Duration of antibiotic therapy after reimplantation	2-4 wk if cultures negative; 12 wk if cultures positive	6 wk
Total duration of antibiotic therapy	6-18 wk	14 wk

*The Liestal algorithm is a well-established approach to the treatment of PJI. According to the type of infection and manifestation, as well as the condition of the implant and the soft tissue or individual problems, the algorithm is used to suggest a pathway for treatment.

As the clinical presentation of PJI varies, a standardized approach to its management does not exist^{6,12}, and it remains challenging to match patients with the Liestal algorithm in daily practice¹⁴. Uncertainties also remain regarding 2-stage exchange, especially concerning the proper use of articulating spacers or the timing of reimplantation and antibiotic administration¹⁵.

At our institution, the 2-stage exchange procedure differs from the current Liestal concept (Table I). We conducted the current retrospective case series study with the hypothesis that our variation in the treatment pathway is a suitable alternative to current strategies.

Materials and Methods

We reviewed the cases all patients admitted for treatment by the 2 hip surgeons (including H.P.N.) at our tertiary referral center during the period of 2003 to 2014 with suspected PJI after total hip arthroplasty (THA). (During the study period, our center performed 400 primary THAs annually, with an adjusted infection rate for THA of 0.2%¹⁶.) A detailed patient medical history, laboratory analyses of inflammatory parameters (C-reactive protein, white blood-cell count), and standard radiographs (pelvic antero-

posterior and cross-table views) were obtained, and preoperative arthrocentesis was performed. The criteria for PJI diagnosis according to the Musculoskeletal Infection Society (MSIS) were applied¹⁷. We included in the study group THA patients with chronic PJI¹⁸ who underwent 2-stage exchange with use of a cement spacer (Fig. 1). All cases in which the patient underwent a different procedure were excluded, in particular, cases of 1-stage revision or cases in which 2-stage exchange was declined or not justified because of the patient's general health, bone quality, or lack of compliance (substance abuse). The latter patients typically underwent a temporary or permanent Girdlestone procedure (Fig. 2).

Once PJI was confirmed or highly suspected, the primary implant and cement (if present) were removed using a stepped trochanteric osteotomy^{19,20}, followed by meticulous debridement and a thorough cleaning of the acetabulum and the medullary cavity. The femur was prepared using conical reamers and the acetabulum, with spherical reamers to clean and prepare the bone for the cement spacer.

If the patient was referred under antibiotic treatment, this was discontinued preoperatively (except in cases of sepsis or a known microorganism and corresponding antibiogram)

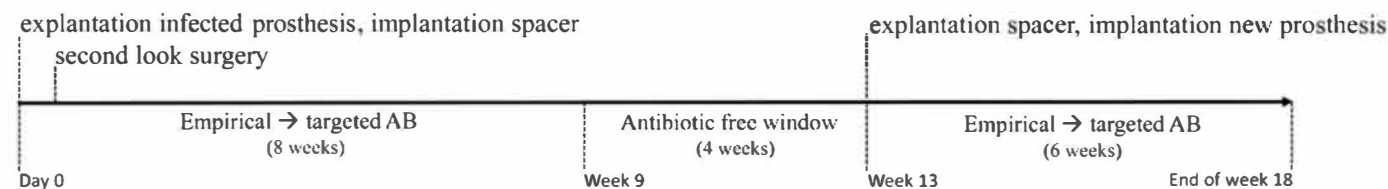


Fig. 1

The timeline of the 2-stage exchange method is shown, with the duration of antibiotic (AB) therapy for each phase indicated. Empirical therapy was switched to targeted upon receipt of biopsy results. If no microorganism was detected on biopsy during reimplantation, the same targeted medication as used after the resection arthroplasty was readministered. A total duration of 8 weeks in the first phase was determined to be appropriate because a normalization of the C-reactive protein (CRP) level was typically reached after 6 weeks, with 2 additional weeks to confirm a stable CRP level. Reasons for a deviation from the intended pattern were infection with multi-resistant organisms, an undesirable clinical healing process, mixed infections, or a lack of normalization of the CRP during the first 6 weeks.

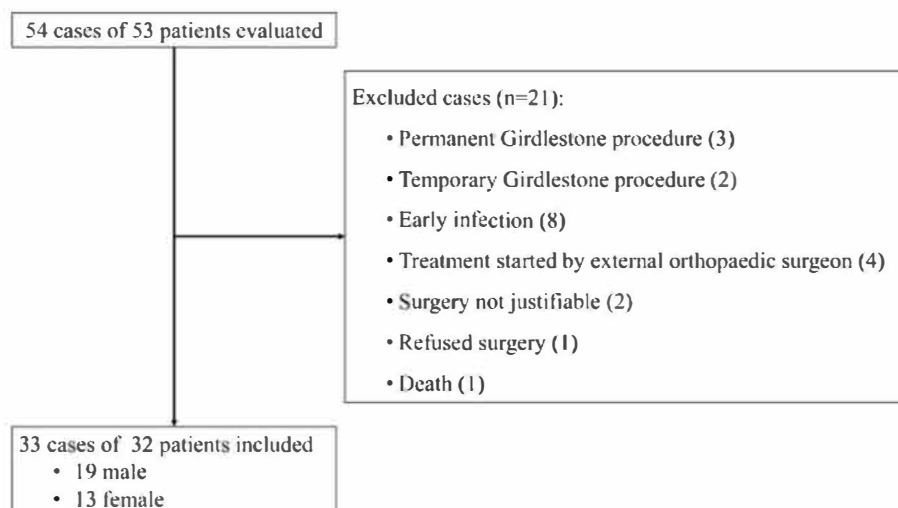


Fig. 2

Patient flow with cohort exclusion criteria and characteristics. The reason for a permanent Girdlestone was very poor bone and/or general health condition, and the reason for a temporary Girdlestone was a lack of compliance due to chronic substance abuse.

for at least 14 days²¹. In addition to 1 biopsy sample for histological analysis, a minimum of 5 samples were obtained intraoperatively for culture and bacterial polymerase chain reaction (PCR) analysis. Some of the removed implants were sent for sonication analysis. Empirical intravenous (IV) antibiotic therapy was administered in all cases involving unknown bacteria. If microbiology results were known, targeted antibiotic therapy was started directly after implant removal and collection of the intraoperative tissue samples, in consultation with our infectious disease specialists.

An individual spacer was customized with antibiotic-loaded bone cement (Palacos; Heraeus Medical) reinforced with bone plates. The femoral head portion and, if necessary, an acetabular part were formed using special molds, taking into consideration the size of the osseous acetabulum, osseous defects, and the need to equalize leg length.

Radiographic images of a sample case are shown in Figures 3-A through 3-F.

A second-look surgery was performed 4 days after removal of the primary implant to further reduce the bacterial load, and it included removal of hematoma and remaining necrotic tissue. During this procedure, the spacer was left untouched. Once the microbiology culture or PCR results were known, empirical antibiotic therapy was switched to targeted eradication therapy.

The third intervention, namely, spacer removal (Fig. 4) and reimplantation, was performed after 4 antibiotic-free weeks if clinical, radiographic, and laboratory results confirmed the absence of infection during this time⁹. A stepped trochanteric osteotomy was again used. Five intraoperative biopsy samples were taken. Empirical IV antibiotic therapy was started and was switched to targeted therapy once the biopsy results were available.

Since the bone stock was impaired in more than half of the cases, bone reconstruction with allograft at the acetabulum was used in 18 cases and impaction grafting at the femoral side

was used in 1 case. In 3 patients, proximal femoral osteotomies were also required to bring the bone closer to the prosthesis, as the medullary cavity at the proximal part of the femur was too wide (Table II).

Outcome Analysis

Each patient was followed regularly for a minimum of 2 years after reimplantation of the definitive prosthesis. Follow-up visits were scheduled for 6 and 12 weeks, 1 year, and 2 years postoperatively or in combination with other routine consultations. The infection-related outcome of healing was defined as the lack of clinical or radiographic signs of infection^{6,9,18,22}. The Harris hip score (HHS) was used to determine functional outcome²³. Other parameters, such as retention of the new prosthesis, death, revision and complications following spacer implantation²⁴, and revision following prosthesis reimplantation, were analyzed²⁵.

Ethical approval for this study was obtained from Kantonale Ethikkommission (KEK) Bern.

Results

Using paper charts and the electronic patient data management system, we identified a total of 54 cases of PJI following THA that were treated by the 2 surgeons during the period of 2003 to 2014. Of those, 21 cases did not meet the a priori-assigned inclusion criteria (Fig. 2). Therefore, 33 cases (32 patients) with chronic PJI treated with a 2-stage exchange were included in the analysis.

The case series included 19 male and 13 female patients with an average age of 67 years. Cohort comorbidities, risk factors for PJI, radiographic characteristics, and local conditions are listed in Table III. Twenty cases in the cohort had ≥ 1 surgical intervention after the primary THA (range, 0 to 30 prior surgical interventions per case). More than 70% of these interventions were due to the PJI. Preoperative arthrocentesis was performed in 31 of 33 cases. In



Fig. 3-A



Fig. 3-B



Fig. 3-C



Fig. 3-D

Figs. 3-A through 3-F Radiographic images of a sample case. **Fig. 3-A** The patient had undergone implant removal and a Girdlestone procedure at another hospital, with persisting sinus tracts after 4 previous attempts to heal the infection. **Fig. 3-B** Status after debridement and cement spacer implantation using a trochanteric osteotomy. **Fig. 3-C** Status after reimplantation of a total hip prosthesis using the same trochanteric osteotomy. **Fig. 3-D** Trochanteric fracture and dislocation 14 days after reimplantation.

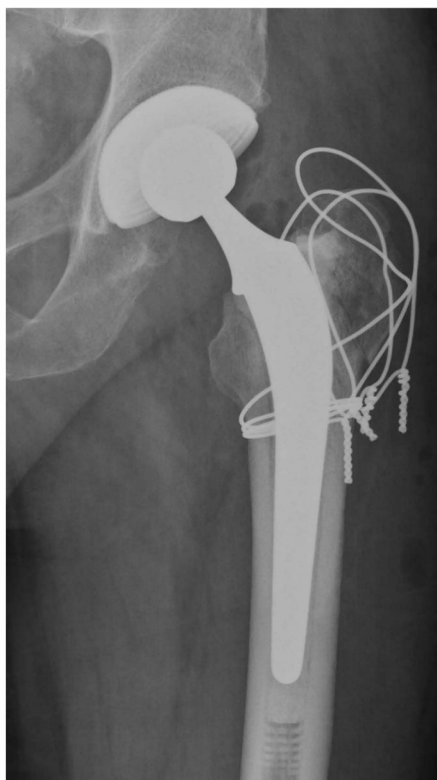


Fig. 3-E



Fig. 3-F

Fig. 3-E Trochanter fixed with use of cerclage wires. **Fig. 3-F** Six years after reimplantation of the hip prosthesis and 5 years after wire removal, the patient had a notable reduction in pain and was unrestricted in his activities. Clinically and radiographically, there were no signs of reinfection or loosening.

1 case, aseptic loosening was suspected, and in another case, infection was already confirmed in a previous operation.

The diagnostic criteria of PJI were fulfilled preoperatively in 25 cases on the basis of the case having met ≥ 1 major criterion for diagnosis and in 8 cases, were fulfilled intraoperatively according to the MSIS criteria defining PJI. In 30 of the 33 cases, empirical IV antibiotic therapy was started after biopsy samples were acquired and explantation of the implants was performed, and was administered for a mean (and standard deviation) of 13 ± 5 days. In 2 cases, the patient received targeted antibiotic therapy 1 week preoperatively following the puncture of an abscess, and in 1 case, targeted antibiotic therapy was started on the day of primary implant removal because preoperative arthrocentesis results were available. After receiving the microbiological results (see Table IV for details), empirical treatment was switched to targeted antibiotic therapy for a mean of 58 ± 15 days, followed by an antibiotic-free window. In the 2 cases in which the antibiotic treatment was started 1 week preoperatively, culture, bacterial PCR, and sonication results were negative. Sonication was used in 15 cases with previous longstanding antibiotic treatment or when results of arthrocentesis were inconclusive. Second-look surgery was performed after an average of 4 days in 31 of the 33 cases. There were only 4 cases in which the patient presented without a notable hematoma (<100 mL) during the second-look surgery. The duration of antibiotic treatment (empirical and targeted) before the antibiotic-free window was an average total of 71 ± 13 days. The antibiotic-free window lasted a median duration of 26 days.

The spacer was in situ for an average of a little more than 3 months (106 ± 25 days).

The analysis of spacer complications showed no notable change of spacer position or notable protrusion in the analyzed cohort. One patient in poor general health and with severe osteoporosis was not included in our analysis despite having a cement spacer, as the spacer protruded during the first week into the pelvic cavity and the case was converted to a permanent Girdlestone.



Fig. 4

Cement spacer at removal after 3 months in situ.

TABLE II Reimplantation Details

	No. of Cases (N = 33)
Fixation	
Cemented	
Stem	17
Cup	9
Acetabular reinforcement ring	6
Uncemented	
Cup	24
Stem	16
Revision stem	14
Bone-grafting (allograft)	
Yes	19
Cancellous bone	12
Structured bone graft	6
Impaction grafting on femoral side	1
No	14
Proximal femoral osteotomy	3

After sample-taking during reimplantation surgery, empirical IV antibiotic therapy was administered in 29 of the 33 cases. In the remaining 4 cases, the primary targeted oral antibiotic therapy was postoperatively continued without empirical antibiotic therapy. Notably, the antibiotics used have a very high bioavailability²⁶. Total antibiotic therapy was maintained for a mean of 47 ± 14 days after reimplantation. Samples taken intraoperatively revealed bacteria in 1 case (1 of 5 biopsies), which was designated as contamination.

The complete antibiotic therapy totaled a mean of 118 ± 18 days, or almost 4 months.

The investigative cohort was followed for a mean of 84 months (range, 29 to 149 months). All patients were free of infection after ≥ 2 years. There were no clinical and mostly no radiographic signs (1 case of aseptic loosening, see below) of reinfection or persisting infection at the most recent follow-up, and the mean HHS was 89. Complications following reimplantation of the new prosthesis are listed in Table V. The retention rate was 94% (31 of 33) at the latest follow-up, at an average of 7 years. Of the 2 cases in which the new implant was not retained, 1 patient developed aseptic loosening, and in the other case, the patient experienced recurrent dislocations. The non-retained implants in these 2 exchange cases were sent for sonification, and the culture results came back negative; both interventions occurred >2 years after reimplantation.

Three deaths were registered after the most recent follow-up, but were all unrelated to reinfection.

Discussion

The main goal when managing PJI is the eradication of infection⁶. We achieved an eradication rate of 100% with our approach. The exclusion criteria may be debated, especially cases in which the patient underwent a Girdlestone procedure. We do not consider the exclusion of 3 cases with poor osseous

conditions and/or pelvic dissociation as a selection bias, because in those cases, the cement spacer bears a high risk of protrusion into the pelvic cavity, necessitating additional and/or more complex surgery. The same applies for the 2 temporary Girdlestone procedures chosen for chronic substance abuse. Instead, we consider the interdisciplinary, thorough planning of the procedure and the inclusion of suitable patients as crucial elements to its success. A minimum 2-year follow-up period was chosen because most exogenously acquired infections occur within 2 years. Following that, infections are mostly caused by hematogenous seeding and are unrelated to surgery^{6,27}. All patients were free of signs of infection at the latest follow-up of at least 2 years, but up to >10 years, after reimplantation. The retention rate was 94%, and reinfection was excluded microbiologically in the 2 new exchanges cases. Our definition of infection-related outcome differs from that of other studies as we do not perform standard laboratory assessments such as C-reactive

TABLE III Cohort Comorbidities, PJI Risk Factors, Local Conditions, and Radiographic Characteristics

Characteristic	No. of Cases (N = 33)
Hypertension	23
Nicotine use	10
Obesity (body mass index ≥ 30 kg/m ²)	9
Diabetes mellitus	9
Presence of a malignancy	4
Radiation therapy	4
Peripheral vascular disease	5
Renal insufficiency	5
Obstructive pulmonary disease	4
Drug-based immunosuppression	2
Rheumatoid arthritis	2
Psoriasis	2
Surgical site infection not involving the affected prosthesis	2
Local signs of infection at primary presentation	8
Warmth, erythema, swelling	3
Sinus tract	4
Abscess	1
Local scarring of soft tissue	9
Normal bone structure	3
Impaired bone structure	30
Prosthesis loosening	25
(Periprosthetic) osteolysis	30
Periosteal reaction	5
Ossification	5
Periprosthetic fracture	2
Diagnosed or highly suspected osteoporosis	3

TABLE IV Microorganisms Identified in Our Cohort

Microorganism	No. [No. of Methicillin-Resistant Pathogens] (%)
Staphylococci, coagulase-negative	12 [7] (36.4)
<i>Staphylococcus aureus</i>	6 [1] (18.2)
Streptococcal species	5 (15.2)
Cutibacterium	4 (12.1)
Mixed infections*	3 [0] (9.1)
Campylobacter	1 (3.0)
Pseudomonas species	1 (3.0)
<i>Serratia marcescens</i>	1 (3.0)

*Mixed infections were (1) coagulase-negative *Staphylococcus* and *Cutibacterium acnes* and *C. avidum*, (2) beta-hemolytic *Streptococcus* and *S. veridians*, (3) *Streptococcus mitis/oralis* and *S. peroris*, *Staphylococcus hemolyticus*, and *Bacillus mycoides*.

protein measurement at 1 and 2-year follow-up^{11-13,28}, but laboratory assessment was performed whenever an infection or reinfection could not be ruled out clinically or radiographically.

We achieved comparable or even higher infection-control rates with our algorithm than in studies in which the Liestal algorithm was used¹¹⁻¹³; nevertheless, a direct comparison remains debatable. The major differences between our orthopaedic surgeons' algorithm and that proposed by Zimmerli et al. are the early introduction (when appropriate) of targeted biofilm-active and oral antibiotic therapy after implant removal even in the presence of a cement spacer, a second-look surgery, and the duration of antibiotic therapy, especially the medium-length duration of postoperative antibiotic treatment and an antibiotic-free window before reimplantation, which is more common in the U.S. than in Europe^{6,9,22}. It is clearly impossible to determine whether one of these aspects is responsible for the different outcome without direct comparison in a prospective randomized controlled trial. However, the use of early targeted oral and biofilm-active antibiotic therapy is controversial, as high bacterial load following initial treatment is associated with the development of antibiotic resistance²⁹. This is greatly feared when treating biofilm-forming staphylococci-associated PJIs³⁰. As shown in studies, hematoma formation is a risk factor for failure³¹. Second-look surgery minimizes devitalized tissue and hematomas and may not only improve wound-healing by lowering pain and swelling but may help to reduce the induction of antibiotic resistance through reduction of bacterial load. This is of central importance after the meticulous debridement during the explantation surgery, which is associated with a higher tendency for bleeding and therefore hematoma formation, as seen in the investigative cohort. The question remains, however, whether functional outcome suffers because of the additional surgery; studies have shown a better functional outcome after a 1-stage compared with a 2-stage exchange¹². With an average HHS of 89 in our series, the results regarding function are as good as in the consulted literature^{12,24,25,28,32}. For 19 hips, the HHS value was >90, an excellent value; for 9, the result was good; and for 4, moderate. The 1 hip with a poor result was in a patient

with PJI and trochanteric pseudoarthrosis on both sides. One hip healed after plate osteosynthesis, and the other with the poor result did not. An inquiry for a preoperative HHS was not performed as we think it is evident that most patients presented in poor functional condition.

We attribute the good functional results to the trochanteric osteotomy, standard or extended, as there is no approach-related additional damage to muscles. In addition, it provides an unobstructed view into the surgical site, enabling an excellent debridement of bone and soft tissues, substantially reducing the bacterial load¹⁹. Nevertheless, one has to be aware that trochanteric pseudoarthrosis may be a complication that is difficult to treat, which must be balanced against the benefits of this approach.

The number of cases presented is relatively small but clearly demonstrates that complex PJIs are treatable long-term and with high reliability. Would a larger number of cases produce worse results? We do not think so, as several cases in our series had been treated unsuccessfully multiple times beforehand. Compared with studies with higher rates of recurrent PJI³³, our series presents a representative group of patients with complex PJIs.

In general we do not know whether an unsuccessful treatment is caused by infection persistence or reinfection³⁴. With stable inflammatory parameters during the antibiotic-free window, infection persistence is largely ruled out. In addition, the antibiotic-free window may help to reduce resistance in the skin microbiome, developed during antibiotic treatment, thereby avoiding reimplantation through an antibiotic-resistant skin flora with the risk of a renewed infection with more resistant organism. To date, there is little information regarding the skin microbiome after antibiotic treatment. Studies on the gut microbiome, however, indicate that recovery can start 7 days after ending antibiotic treatment but it may take years to restore fully³⁵⁻³⁷.

The continuation of antibiotic treatment after reimplantation is controversial. Several studies report low levels of persistence or reinfection with only a prophylaxis³⁸ or brief³⁹ antibiotic therapy. However, other studies have found clear advantages of extended antibiotic therapy for between 4 weeks⁴⁰ and 3 months^{41,42}. Our duration of therapy was generally mid-range, with no infection persistence or reinfection and an eradication rate of 100% over an average of 7 years, similar to Fink et al.^{32,43}.

Prolonged antibiotic administration seems to be advantageous, especially in reconstructions using allograft, which was used in more than half the cases in our series⁴⁴. In spite of

TABLE V Complications After Reimplantation

Complication	No. of Cases (N = 33)
Dislocation of the prosthesis	2
Dislocation of the trochanter or nonunion of the osteotomy	5
Aseptic loosening	1
Nerve lesions	0
Vascular damage	0

several large allografts (including impaction grafting), there was no reinfection, even in areas previously irradiated for tumors. This supports our regimen of IV antibiotic therapy for 14 days followed by 4 weeks of oral antibiotics in these cases.

Nevertheless, in the absence of infection persistence at the time of reimplantation and in the absence of allografts, antibiotic therapy equal to the incubation period of the samples (14 days) may be sufficient³⁹. Unquestionably, further investigation and studies are needed here.

Conclusions

A meticulously performed 2-stage exchange for PJI with early targeted antibiotic treatment (oral, if applicable), a second-look surgery, an antibiotic-free window before reimplantation, and a medium-term interval of antibiotic treatment post-reimplantation showed a high level of success in this treatment pathway variation and may serve for further investigations to elucidate the influence of the different parameters on successful treatment. ■

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