Evaluation of an interdisciplinary therapy algorithm in patients with prosthetic joint infections

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Abstract

Purpose Current concepts in the treatment of prosthetic joint infections include prosthetic retention and exchange strategies according to published recommendations. A useful algorithm should fit for each type of prosthetic joint infection, even the most complicated situations. We present the outcome of 147 patients with prosthetic joint infections of the hip or the knee joint in an unselected population in clinical routine.

Methods Between November 2006 and November 2009, 147 consecutive patients with prosthetic joint infections of the hip or knee were treated according to an algorithm based on the concept published by Zimmerli et al. in 2004. Causative organism, duration of infection, patient comorbidities, surgical treatment, antibiotic treatment, and outcome of treatment were analysed retrospectively. According to the criteria duration of

infection, stability of prosthesis, local and systemic risk factors, and susceptibility of the causative pathogen, patients were treated either with debridement and retention or a long-interval two-stage procedure.

Results A pathogen could be detected in 82.8 % of the patients, gram-positive cocci being most common. Twenty-seven patients were treated with debridement and retention and 120 were treated with a two-stage procedure. In 68 cases difficult-to-treat pathogens could be detected, a polymicrobial infection was found in 51 patients. Definitely free of infection were 71.6 % after a two-stage procedure, and 70.4 % after debridement and retention.

Conclusions Our data indicates that the applied algorithm is suitable to be applied as a day-to-day routine, and we confirmed that published results from the literature can be reproduced in an inhomogeneous patient cohort.

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Introduction

Periprosthetic joint infections (PJI) after total joint replacement are a severe complication resulting in high morbidity for the patient as well as extensive costs for the health care system [1, 2]. The frequency of PJI is estimated to be 0.4–2 % in primary total arthroplasty [3], rising up to 5–15 % in high risk patients and in revision surgery [4–6].

A valid and standardized diagnostic procedure including clinical, laboratory, microbiological and histopathological findings is essential to differentiate between aseptic loosening and PJI [6–8]. The differential diagnostics between a septic condition or an aseptic loosening remains difficult [9]. With a suspected PJI, surgical eradication of the pathogen must be combined with an effective and targeted antimicrobial therapy. Surgical options include debridement and

retention in cases of acute infection, or a complete exchange of the implant in a one-step or two-step approach in cases of chronic infection [6, 10, 11].

An important requirement of the one-stage revision procedure is the detection of the causative pathogen. Pre-operative joint aspiration is the only mean to acquire suitable material for pathogen detection, but one out of five infections remain unrecognized by this method [12]. Without pathogen detection, targeted antimicrobial therapy is impossible and the chances of eradication are diminished. Miscalculated antibiotic treatment can involve the potential induction of “small colony variants” or the development of resistances [13]. The strategy of a one-step exchange therefore remains under controversial discussion. To assure the best possible pathogen detection and subsequently the most effective antimicrobial therapy, most centres in North America prefer a two-stage revision procedure [4, 6], making use of intra-operatively obtained specimens to detect the causative pathogen, and adjusting the antibiotic therapy accordingly. This approach is quoted in the literature to be successful in up to 87 % of cases [14].

To standardize the decision-making process for the surgeon, therapy algorithms have been established in the past, with the “Liestal concept” probably being the best known and most used one. In small collectives and under the very defined conditions of a study centre, cure rates of 90 % and more for PJI are reported [15]. Patients treated according to this algorithm are reported to have a better clinical outcome [16]. While the “Liestal concept” considers infect duration, causative pathogen and prosthesis stability to decide upon the best surgical treatment option, local and systemic risk factors and the comorbidities of the patients are not taken into account. In clinical routine, polymorbid patients with missed or delayed diagnostics, insufficient pretreatment and late referral are hard to fit into any scheme of an algorithm. Nevertheless these patients are more rule than exception since patients are often pretreated by non-specialized centres, i.e. with arthroscopic debridements only or insufficient antibiotic therapy.

Following this rationale, and considering the lack of published results of larger and unbiased cohorts, we here present our experience and outcome, employing the treatment algorithm in clinical routine and a large cohort of 147 patients. Our hypothesis was that the algorithm is suitable and robust enough to be applied to a day-to-day routine, and that the results from the literature can be reproduced in an inhomogeneous patient cohort.

Methods

Between November 2006 and November 2009, 147 consecutive patients with proven PJI of the hip or knee were treated

in our institution by a standardized therapy algorithm based on previous works of Zimmerli et al. [6, 15]. Based on the literature [3, 4, 6, 8, 17], we slightly modified the Liestal algorithm and adapted it to our patients and needs (see below and Fig. 1).

No patients were excluded. Routine clinical data was collected and analysed retrospectively as anonymized aggregate data, thus no consent had to be obtained in accordance with appropriate regulations. For outcome evaluation, all available data from the follow-up visits in the outpatient clinic were used. To represent the full spectrum of PJI, no patients were excluded, regardless of risk factors, previous infections or operations, unsuccessful treatment attempts in the past or septic conditions. All patients underwent standardized diagnostics with physical examination and laboratory tests, including serum C-reactive protein (CRP) and white blood cell count (WBC) as well as medical case history.

Joint aspiration was conducted under strictly aseptic conditions, as recommended, using a spot incision and avoiding administration of local anaesthetics into the joint. Antibiotics were not administered until specimens were obtained for microbiological testing. Time of incubation was extended from ten to 14 days to enhance sensitivity [18]. In chronic cases when antibiotics had already been administered by the transferring hospital, and if clinically possible, treatment was paused for two to four weeks to avoid pathogen suppression in microbiological testing. This pause was shortened in cases of urgent need of surgical treatment. The joint aspirate was incubated in aerobic, anaerobic, and fungal blood culture bottles as published [19].

Synovial fluid was examined cytologically according to descriptions by Trampuz et al. [20]. White blood cell count and cell differentiation were performed by a blood count analyser in body fluid mode.

Intra-operatively, at least five tissue specimens were taken from representative areas showing signs of infections, and each was bisected to be analysed microbiologically and histopathologically. Processing of histological tissue specimens was performed according to the criteria of Mirra et al. [21] with formalin fixation, paraffin embedding and neutrophil counts in the sections.

A PJI was considered proven if at least one of the following criteria was fulfilled [16]:

1. Purulent synovial fluid or more than 1700 leukocytes/ μ l or more than 65 % neutrophile granulocytes in the joint aspirate [20]
2. Histological confirmation of an acute inflammation reaction with more than five neutrophils / „high power field“ in five representative areas [21, 22]
3. Pathogen detection in sterile joint aspiration or in at least two intra-operative tissue specimen after incubation
4. Definite signs of PJI clinically or intra-operatively (e.g. sinus tract) [6]

Fig. 1 Treatment algorithm

Based upon the published algorithms [6, 15, 23], we have slightly adapted the algorithm to our own standards and requirements. The following criteria were used to decide upon the therapeutic procedure, and an overview of the therapy algorithm applied is shown in Fig. 1.

PJI were classified as acute (symptoms shorter than three weeks) or chronic infections (symptoms longer than three weeks), as determined by the onset of the first symptoms. Systemic and local risk factors (soft tissue conditions) were graded pre-operatively according to the classification of McPherson et al. [23]. Loosened prostheses were always explanted; stable ones were explanted if symptom duration exceeded three weeks. Upon detection of any of the pathogens listed in Table 1, PJI were classified as “difficult-to-treat” [6, 8, 24].

All open surgical procedures included debridement with extensive synovectomy, intra-operative examination of non-osseointegrated prosthesis stability, exchange of all non-osseointegrated components, intensive irrigation, and drainage for three to five days. Antibiotic therapy was chosen according to the detected pathogen and administered i.v. for at least 14 days, followed by oral therapy for six weeks to three months in cases of hip prostheses and six months in cases of knee prostheses according to the published recommendations [6, 8, 25].

Debridement and retention of prosthesis was performed mainly in acute infections [26] when implants were stable, soft tissues intact, and bactericidal antibiotics effective against the detected pathogen were available [6]. Chronic or recurrent

infections were treated in a two-stage exchange procedure. No one-stage exchanges were performed. The infected prosthesis was explanted followed by an extensive surgical debridement as described above. Antibiotic therapy was administered intravenously for at least 14 days, followed by oral therapy for six weeks. After a treatment pause of two weeks, joint aspiration was conducted for microbiological examination. Reimplantation was performed when aspirate was sterile and

Table 1 Pathogens detected

Pathogens	Description
„Small colony variants“ (SCV)	Staphylococci show phenotypical resistance against many antibiotics
Enterococci	No oral bactericidal therapy regimen available
<i>Pseudomonas aeruginosa</i>	Fast resistance development under mono therapy; no oral bactericidal therapy regimen available in chinolone resistant <i>pseudomonas</i> species, biofilm production
<i>Fungi</i>	Biofilm production; no therapy against adhering fungi
<i>MRS</i>	Methicillin-resistant Staphylococci
<i>VRE</i>	Vancomycin-resistant Enterococci
<i>CRE</i>	Chinolone-resistant Enterococci
<i>CRP</i>	Chinolone-resistant <i>Pseudomonas</i>
<i>ESBL</i>	Extended-Spectrum-Betalactamase producing Enterobacteriaceae
<i>RR</i>	Rifampicin-resistant gram positive pathogens; no oral bactericidal therapy with biofilm activity

no systemic signs of infection were seen ($\text{CRP} < 10 \text{ mg/l}$, $\text{WBC} < 10.2 \text{ G/l}$). In cases of pathogen detection, further surgical debridement was performed, and antibiotic therapy was continued for six weeks (14 days intravenously, followed by four weeks per os). In cases of pathogen detection from samples acquired during re-implantation, debridement and retention of the prosthesis was performed, followed by a six- to twelve-week antibiotic therapy according to the susceptibility pattern of both implantation and re-implantation pathogens.

Decision on a suitable antibiotic therapy was made in an interdisciplinary case discussion at the beginning of therapy, according to the detected pathogen and its susceptibility pattern as well as to published recommendations [6, 8, 25, 27].

Weekly interdisciplinary case discussions and rounds (orthopaedic surgeon and clinical microbiologist) were held to optimize treatment for our patients. Surveillance of kidney and liver function, as well as drug monitoring (vancomycin and gentamicin levels) was part of our standard protocol.

The outcome was defined according to Laffer et al. [16]:

- „*Definitely free of infection*“: No signs of infection, $\text{CRP} \leq 10 \text{ mg/l}$, follow-up $\geq$ two years
- „*Probably free of infection*“: No signs of infection but $\text{CRP} \geq 10 \text{ mg/l}$ or follow-up $<$ two years
- „*Treatment failure*“: Persistence or recurrence of PJI with the same or an unknown pathogen during or after the completion of antimicrobial therapy
- „*Probable treatment failure*“: Possible persistence or recurrence of infection, not matching the strict criteria for a PJI
- „*New Infection*“: Infection by an initially undetected pathogen
- „*Death because of PJI-associated sepsis*“: Death as a result of a PJI-associated sepsis
- „*Death (other reasons)*“: Death unrelated to PJI
- „*Permanent explantation or amputation*“: The affected joint could not be restored

For the data analysis, all recorded data from the patient files were digitized and exported to MS Excel 2007 (Microsoft, Redmond, WA, USA) and GraphPad Prism 5.04 (GraphPad Software, Inc., La Jolla, CA, USA). Individual comparisons were analysed using chi-square cross tabulations and the corresponding Fischer exact test, which determined the likelihood coefficient.

Results

In our evaluation 147 patients with 147 prostheses (90 hips, 57 knees) were included. The mean duration of infection before start of our therapy algorithm was 83.9 ± 81.4 days

(range, three to 720 days). In 25 patients (17 %) infection was classified as acute, and 122 patients (83 %) suffered from chronic infection. Before the start of therapy in our institution, a mean number of 1.6 ± 2.4 (range, 0–17) revisions had been performed.

Twenty patients (13.6 %) showed signs of a SIRS, six patients (4.1 %) suffered from a manifest sepsis at the time of inclusion in our study, according to the ACCP criteria [28]. Only 12 patients (8.2 %) with a known causative pathogen had been treated with an adequate antibiotic therapy prior to the start of the study regime, while 59 patients had received an inadequate antibiotic therapy prior to treatment in our institution. Table 2 summarizes patient data.

Preoperative joint aspiration and long-term incubation detected a pathogen in 89 cases (sensitivity 60.5 %), and in the intraoperatively gained specimens in 122 cases (82.9 %). The germ detected preoperatively and intraoperatively matched in 87 cases (71.3 %) and varied in 35 cases (28.7 %). In 25 cases (17 %), no pathogen was detected in any analysis. Table 3 illustrates the pathogen distribution of all PJI. The histopathological findings [21] provided qualitative proof of a PJI in 110 cases (74.8 %).

In 27 cases (18.4 %) we performed surgical debridement with retention. The prior clinical symptoms were present for 17.3 ± 18 days (three to 97 days), in 21 cases (77.8 %) $<$ three weeks, and in six cases (22.2 %) $>$ three weeks. Retention was performed against our pre-defined algorithm in these six cases due to the explicit wish of our patients and after extensive education. Only one of them sustained a long-term retention, with three surgical debridements and long-term antibiotics administered for six months.

A two-stage revision was performed in 120 cases (81.6 %). The time interval between the first revision and the re-implantation was 109.9 ± 39.6 days (56–379 days). During the interval without endoprostheses 3.3 ± 3.6 (range zero to 17) additional revisions had to be performed to consolidate the

Table 2 Patient data

Demographics	Retention	Two-stage exchange
Total, <i>n</i> [%]	27 [18.4 %]	120 [81.6 %]
Mean age [min – max]	69.1 ± 11.9 [58–80]	68.3 ± 12.0 [22–89]
Knee, <i>n</i> [%]	7 [25.9]	50 [41.6]
Hip, <i>n</i> [%]	20 [74.1]	70 [58.3]
Male, <i>n</i> [%]	9 [33.3]	66 [55]
Female, <i>n</i> [%]	18 [66.6]	54 [45]
Mean follow-up, month [range]	27.8 ± 14.8 [1–56]	29 ± 11.3 [4–56]
BMI, kg / m^2 [range]	25.7 ± 4.1 [19–35]	26.92 ± 6 [15–45]
ASA-score [range]	2.4 ± 0.6 [1–3]	2.5 ± 0.7 [1–4]
Acute infection, <i>n</i> [%]	21 [84 %]	4 [16 %]
Chronic infection, <i>n</i> [%]	6 [5 %]	116 [95 %]

Table 3 Pathogen distribution

Pathogen	Retention (<i>n</i> =27)	Two stage exchange (<i>n</i> =120)
<i>S. aureus</i> , <i>n</i> [%]	4 (14.8 %)	11 (9.2 %)
CNS, <i>n</i> [%]	8 (29.6 %)	19 (15.8 %)
Streptococci, <i>n</i> [%]	0 (0 %)	3 (2.5 %)
Gram negative Bacilli, <i>n</i> [%]	1 (3.7 %)	3 (2.5 %)
MRSA/MRSE, <i>n</i> [%]	2 (7.4 %)	11 (9.2 %)
Enterococci, <i>n</i> [%]	1 (3.7 %)	5 (4.1 %)
Candida, <i>n</i> [%]	0 (0 %)	5 (4.1 %)
ESBL, <i>n</i> [%]	0	1 (0.8 %)
No pathogen detected, <i>n</i> [%]	4 (14.8 %)	21 (17.2 %)
Polymicrobial infections, <i>n</i> [%]	8 (25.9 %)	41 (34.6 %)

infection. In 50 cases (41.7 %) a spacer was implanted (27 knees, 23 hips).

Antibiotics were administered intravenously for 38.1 ± 38.6 days (14–290 days) followed by an oral therapy for 47.4 ± 22.9 days (28–180 days) (debridement with retention: 97.4 ± 49.4 days [28–180 days] i.v., 28.3 ± 18 days [14–85 days] p.o.). The antibiotic and surgical therapy had to be adjusted to the individual patient requirements in 62 cases (41.9 %), as determined in our interdisciplinary case discussions and based on the published therapy recommendations [6, 8, 25].

Follow-up after the first surgical intervention was 29.2 ± 11.3 months. The outcome is summarized in Table 4. Definitely free of infection were 86 (71.7 %) after a two-stage procedure, and 19 (70.4 %) after debridement and retention ($p=0.191$). In total, 105 of the 147 (71.4 %) patients included in our study were graded as “definitely free of infection” (follow-up 31.9 ± 9.0 months [24–56 months]), and eight (5.4 %) as “probably free of infection” (follow-up 23.9 ± 6.6 months [12–34 months]). No new infection was seen during the follow-up. A “definitive treatment failure” was detected in five cases (3.4 %) within the first year and four more cases (2.7 %) during the second

year. Five patients (3.4 %) died as result of a PJI-associated sepsis and four patients died for other reasons.

Discussion

The correct treatment of PJI remains a clinical challenge in orthopaedic surgery. A useful algorithm should fit for each type of PJI, even in the most complicated situations. However, treatment algorithms are often devised from cohorts with well-defined conditions. This includes quick and thorough diagnostic, fast referral into a specialized centre and treatment according to the algorithm right from the beginning. Additionally, local and systemic risk factors have to be taken into consideration to improve the outcome and provide extra care when needed. Clinical reality, however, is often different. The first presentation of patients with a painful endoprosthesis is often with his general physician, and symptoms can be obscured by other overlying problems. Without the backup of a specialist, diagnostics are oftentimes delayed and incomplete, and the subsequent therapy is bound to be insufficient. The implementation of algorithms seems beneficial to establish clinical recommendations that can be followed even by the non-expert. Even though established for hip and knee joint prostheses, and suggested for other PJI [29, 30], very few data is available on the actual implementation in clinical routine [4, 5, 7, 12]. We are therefore presenting the results of our PJI algorithm in clinical day-to-day routine on a collective of 147 cases without selection bias or exclusion criteria.

Classifications of PJI are inconsistent in literature [15, 16, 20–23, 31, 32]. Nevertheless, a differentiation between acute and chronic PJI seems established, setting the cut-off at three weeks of duration of symptoms before the onset of therapy [6]. The correct assessment of the duration of the infection is crucial to follow the correct path in the algorithm. Per se, the outcome in chronic or acute infections was much the same in our collective. In cases of doubt, we advise towards treating the infection as a chronic PJI with more radical treatment and two-step exchange.

Any strategy of curing an infection must combine surgical debridement with antibiotic treatment. Debridement and retention is usually reserved for acute infections, but the success rates of this procedure are evaluated inconsistently and vary considerably between eight and 83 % [33, 34]. A stable implant, no more than two systemic risk factors, no or little damage in the soft tissue, no recurrent infection, and no detection of difficult-to-treat pathogens are a precondition for the retention of a prosthesis [6, 15, 35]. While some centres even extend the indication of this procedure into chronic prosthesis with sensitive pathogens, others have left this concept entirely. We find in our study that both procedures have their valid indications.

Table 4 Patient outcomes

Outcome	Retention	Two-stage exchange	Total patients
Definitely free of infection	19	86	105
Probably free of infection	0	8	8
Definite treatment failure	4	5	9
Probable treatment failure	3	13	16
Death of PJI-associated sepsis	1	4	5
Death (other reason)	0	4	4

If applied to the correct cases, debridement and retention can achieve a cure rate that is comparable to that of a two-stage exchange. However, only 27 of the patients in our collective matched the criteria to be eligible for this procedure. It is generally agreed that sole debridement and retention is not adequate in patients with sinus tracts or heavily damaged soft tissue as these are signs of a chronic infection. Superinfections must be assumed and soft tissue closing can be complex [6, 35]. High failure rates (84 % for knee and 80 % for hip PJI) have been described in patients with PJI caused by difficult-to-treat pathogens and treated with debridement and retention [36, 37]. Our data shows that a “definitively free of infection” state after debridement and retention in cases where a difficult-to-treat pathogen was detected in the intraoperative samples, could then be achieved in only five out of 12 cases (42 %), although the mean time from onset of symptoms until debridement was only ten (range five to 15) days. Therefore, in an acute PJI caused by difficult-to-treat pathogens or in patients with multiple systemic risk factors an immediate explantation of the prosthesis and a two-stage exchange should be considered.

In patients with chronic PJI, high rates of re-infection (up to 61 %) have been published for debridement and retention [38]. In our collective, debridement and retention in chronic infection was successful in only 16.6 % (one out of six), while two-stage exchange was successful in 78.3 % (94 out of 120). We therefore agree that these patients should be treated with two-stage exchange of prosthesis [6, 8].

Detection of difficult-to-treat pathogens is a considerable parameter for treatment failure [36, 39]. As in debridement and retention, also in two-stage exchange, the outcome was worse in patients with detection of difficult-to-treat pathogens ($n=56$) compared to those without ($n=64$) (infect free rate 60.7 % vs. 93.7 % [$p<0.001$]), and significantly more revisions between explantation and reimplantation were necessary (5.3 ± 3.9 vs. 1.8 ± 2.5 [$p<0.001$]). Our data is supported by the literature [36, 39]. Hanssen [40] reports re-infection rates of 22 % in patients with hip infections due to difficult-to-treat pathogens ($n=9$, MRSA) and treated with two-stage exchange. Mittal [41] reports recurrence rates of 24 % for knee infections ($n=25$ MRSA; $n=12$ MRSE); Kilgus [39] demonstrates more surgical revisions in treating infections caused by methicillin-resistant ($n=19$) vs. methicillin-susceptible bacteria ($n=16$) [3.4 vs. 2.9 revisions].

In addition to surgical debridement, standardized antibiotic therapy is the key to success in the therapy of PJI [6, 8]. Debridement and retention and a two-stage exchange with spacer implantation are only indicated if antibiotics with high biofilm activity are available for the detected pathogen [6, 42, 43]. Antibiotic therapy should therefore combine bactericidal substances with those having biofilm activity (i.e. Rifampicin) [44]. The optimal procedure remains unclear if no agents are available matching these standards (e. g. rifampicin-resistant

gram-positive species or ciprofloxacin-resistant gram-negative species). Other antibiotics like Fosfomycin, Daptomycin, Moxifloxacin, and Tigecyclin also show activity against biofilms [44, 45], and they find their role in treatment of PJI in appropriate combinations.

Empiric antibiotic therapy was chosen according to the anticipated pathogens in our institution. After pathogen detection, adaption of antibiotic therapy according to the susceptibility profile, individual patient’s needs and considering published therapy recommendations [25] was necessary in 31 %. Because of the complexity of PJI such adjustment of antibiotic therapy in an interdisciplinary team based on standardized therapy algorithms seems essential [6, 46].

Our hypothesis was that the applied algorithm is suitable and robust enough to be applied to a day-to-day routine. We successfully evaluated and confirmed the treatment algorithm in our study population. In total, we can report a total cure rate of 77 % (definitively free of infection and probably free of infection; 113 out of 147 patients). This is lower than numbers reported by some, but other groups found similar rates in clinical routine collectives [47], confirming that the results from the literature can be reproduced in an inhomogeneous patient cohort.

Limitations

We acknowledge that our study has limitations. The sample size is low for a study investigating arthroplasties, even though the number of patients is high for the treatment of PJI in infected TKAs and THAs. Additionally the data was gathered retrospectively only, limiting quality and level of evidence. The inhomogeneity of the patients investigated is both a weakness and a strength of the paper. Patients with PJI are complex and difficult to compare, but this represents day-to-day clinical experience. Future prospective trials with a higher number of patients seem essential to confirm our findings. Eventually, new risk scores and a further modification of the published therapy algorithms may become necessary.

Conclusion

We have presented one of the largest patient collectives published so far investigating the outcome of 147 patients with prosthetic joint infections of the hip or the knee joint in an unselected population in clinical routine based on published recommendations. Our data indicates that the applied algorithm is suitable to be applied to a day-to-day routine, and we confirmed that published results from the literature can be reproduced in an inhomogeneous patient cohort.

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