Dissertation

Clinical outcome and microbiological findings using antibiotic loaded spacers in two-stage revision of periprosthetic hip and knee joint infections

submitted by

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for the Academic Degree of

Doctor of Medical Science (Dr. scient. med.)

at the

Medical University of Graz

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under the supervision of

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2016

Declaration

I hereby declare that this dissertation is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this dissertation. Due acknowledgement has been made in the text to all other material used. Throughout this dissertation and in all related publications I followed the guidelines of “Good Scientific Practice”.

Graz, 3.11.2016

Dedicated to all my beloved ones who always supported me on my personal journey

Acknowledgements

At first, I'd like to thank Univ.-Prof. Dr. Andreas Leithner, not only for giving me the opportunity to join his amazing team, but also for his continuous support and guidance throughout my training.

Furthermore, I'd like to thank the members of my doctoral committee, Assoc. Prof. Priv. Doz. Mathias Glehr and Univ.-Prof. Dr. Gerold Holzer for their valuable comments, input and guidance.

I'd like to thank Dr. Norbert Kastner and Assoc. Prof. Priv. Doz. Mathias Glehr for their help and support concerning clinical questions and patient care with regard to the special topic of periprosthetic joint infections.

Special thanks to Mag. Gerold Schwantzer from the Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, for the statistical analyses.

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List of Abbreviations

AAOS	American Academy of Orthopaedic Surgeons
CRP	c-reactive protein
CT	computed tomography
DAIR	debridement, antibiotics and implant removal
ESR	erythrocyte sedimentation rate
IDSA	Consensus Society of America
IL-6	serum interleukin
IQR	interquartile range
MRI	magnetic resonance imaging
MSIS	Musculoskeletal Infection Society
PET	positron emission tomography
PGI	Periprothetische Gelenksinfektion
PJI	periprosthetic joint infection
PMMA	polymethyl methacrylate
SD	Standard deviation
THA	total hip arthroplasty
TKA	total knee arthroplasty
WBC	white blood cell count

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Abstract

Background: Total knee- and hip arthroplasty (TKA, THA) are considered to be successful treatment strategies for osteoarthritis of the knee- and hip joint. However, the constantly increasing number of joint replacements is accompanied by a rising number of prosthetic joint infections (PJI) as well. With a reported incidence of less than one percent after primary hip- and less than two percent after primary knee replacement - and a considerable higher rate after revision surgery - PJI represents one of the leading causes for revision following total joint arthroplasty of the lower extremity. Therefore, the management of PJI remains a challenging task, as adequate treatment strategies seem to be mandatory to avoid irreversible damage of the affected joint or further systemic complications. Two-stage revision arthroplasty, including implant-removal and the implantation of an antibiotic-loaded cement spacer, followed by revision arthroplasty later on, seems to be the procedure of choice in cases of PJI, especially for late, chronic infections. Although this procedure is well described in the literature, the results remain unpredictable due to various clinical findings and the absence of prospective randomised trials. We analysed (1) mortality and (2) reinfection rates in a series of patients who underwent two-stage revision surgery for periprosthetic hip- and knee joint infections. Furthermore, we maintained a special focus on the (3) length of spacer-retention and its impact on the outcome in order to determine the optimal time for second-stage surgery.

Patients and Methods: A consecutive series of 76 patients with periprosthetic hip- and 77 patients with periprosthetic knee joint infections, who had undergone two-stage revision arthroplasty for PJI between 2005 and 2013, were included into the study. Classification of infection was performed according to the system developed by the Workgroup of the Musculoskeletal Infection Society. Antibiotic loaded cement spacers were used for all of the patients.

Results: The mean spacer-retention period was 12.6 weeks for prosthetic hip- and 10.6 weeks for prosthetic knee joint infections. One or more additional spacer exchanges were necessary in 13 (9.9%) and 17 (22.3%) cases due to positive

signs of persisting infection in the frozen section and suspect intra-operative findings. After a mean overall follow-up time of 20.5 and 35 months, PJI has reoccurred in 19 (30.3 %) versus 14 (18.7%) patients. For PJI of the hip, spacer-retention periods of more than eleven or less than 4 weeks have led to a significant worse outcome. The best outcome was achieved in patients who had undergone second-stage surgery after 4-11 weeks. 90% of these patients remained free of infection until final follow-up.
For prosthetic knee joint infections, it could be proven that a prolonged spacer-retention period of more than 83 days has led to a significant higher proportion of reinfections. Furthermore, it could be seen that significant compromising local conditions of the periprosthetic tissue and surrounding skin, as well as repeated spacer-exchanges between the first- and second-stage procedure, have influenced the outcome negatively. No significant influence on the outcome regarding re-infection rates could be determined for patients' age or gender.

Conclusions: According to our findings, the optimal time for second-stage procedure could be calculated between four and eleven weeks for hip joint infections and less than 12 weeks for PJI of the knee. To our knowledge, this study is the first focusing on the length of spacer retention and its potential impact on the outcome within the setting of two-stage revision arthroplasty for PJI. Nonetheless, given the clinical significance and the expected increase of PJI in the nearer future, further, essentially prospective studies would be desirable.

Abstract in German (Zusammenfassung)

Hintergrund: Periprothetische Gelenksinfektionen (PGI) zählen zu den häufigsten Ursachen für Revisionsoperationen nach Totalendoprothesen der großen Gelenke und sind nach wie vor mit einer hohen Morbiditäts- und Mortalitätsrate vergesellschaftet. Trotzdem gibt es keinen einheitlichen Konsens hinsichtlich Therapieempfehlungen in der aktuellen Literatur.
Der zweizeitige Wechsel, unter Zuhilfenahme eines temporär eingebrachten antibiotika-augmentierten Gelenkspacers, ist eine gut beschriebene und weit verbreitete Therapiestrategie bei PGI. Obwohl mit Erfolgsraten von bis zu 80% beschrieben, bleiben die Resultate nach zweizeitigem Wechsel unvorhersehbar und sind daher schwer zu standardisieren. Dies könnte sowohl an der großen Varianz hinsichtlich des klinischen Bildes, der mikrobiologischen Ergebnisse als auch der Operationsmethoden liegen, hier seien insbesondere die beträchtlichen Unterschiede in der beschriebenen Verweildauer des Gelenkspacers erwähnt.

Patienten und Methoden: Ausgehend von der Hypothese, dass es eine optimale Zeitspanne für die Explantation des Gelenkspacers bzw. die Revisions-Operation gibt, haben wir die Daten von 76 Patienten mit periprothetischen Hüft-, sowie jene von 77 Patienten mit periprothetischen Kniegelenksinfektionen, welche zwischen 2005 und 2013 mittels zweizeitigem Verfahren behandelt wurden, retrospektiv analysiert. Wir untersuchten (1) die Mortalitätsrate, sowie (2) die Reinfektionsrate nach stattgehabtem zweizeitigen Prothesenwechsel in Abhängigkeit von der (3) Spacer-Verweildauer. Die Einteilung der periprothetischen Gelenksinfektionen erfolgte nach der Klassifikation der Arbeitsgruppe für muskuloskelettale Infektionen. Die Erstoperation beinhaltete die Explantation sämtlicher Prothesenkomponenten sowie das radikale Débridement potentiell infizierter Weichteile. Daraufhin wurde ein temporärer Gelenkspacer implantiert. Die Zweitoperation (Revisions-Arthroplastik) wurde nach Infekteradikation durchgeführt.

Ergebnisse: Nach einem durchschnittlichen Nachuntersuchungszeitraum von 20.5 bzw. 35 Monaten kam es bei 19 (30.3 %, Hüften) versus 14 (18.7%, Knie) zu einer Reinfektion. Die durchschnittliche Spacer-Verweildauer betrug 12.6 Wochen für PGI der Hüft- und 10.6 Wochen für PGI der Kniegelenke. Ein oder mehrere Spacer-Wechsel wurden in 13 (9.9%) und 17 (22.3%) Fällen, aufgrund von positiven Zeichen einer persistierenden Infektion oder suspekten intraoperativen Befunden, notwendig.

In 40 Fällen dauerte die Spacer-Periode 4 bis 11 Wochen, in 5 weniger als 4 Wochen und in 23 Fällen länger als 11 Wochen.

Das beste Outcome hinsichtlich langfristiger Infekteradikation bei prothetischen Hüftgelenksinfektionen konnte für einen Zeitraum von vier bis elf Wochen zwischen erster- und zweiter Operation beobachtet werden. Kürzere bzw. deutlich prolongierte Spacer-Verweilzeiten führen zu einem signifikant schlechteren Ergebnis. Für Kniegelenksinfektionen konnte nachgewiesen werden, dass eine Spacer-Verweildauer von mehr als 83 Tagen zu einer signifikant höheren Rate an Reinfektionen führt.

Schlechte lokale Haut- bzw. Wundverhältnisse, sowie wiederholt durchgeführte Spacer-Wechsel zwischen Erst- und Zweitoperation beeinflussten das Outcome ebenfalls negativ. Das Patientenalter oder -geschlecht hingegen schienen keine Auswirkungen auf die Ergebnisse nach zweizeitigem Prothesenwechsel zu haben.

Schlussfolgerungen: Unseren Erkenntnissen zufolge liegt der optimale Zeitraum für die Revisions-Arthroplastik als abschließende Operation eines zweizeitig durchgeführten Prothesenwechsels zwischen vier und elf Wochen bei Hüftgelenken. Bzw. unter 83 Tagen bei Kniegelenken. In diesen Zeiträumen konnten die signifikant besten Ergebnisse hinsichtlich langfristiger Infekteradikation erzielt werden.

Nach unserem Wissen ist dies die erste Studie, die den Fokus auf den Einfluss der Spacer-Verweildauer, im Rahmen eines zweizeitigen Prothesenwechsels bei PGI, auf die Ergebnisse hinsichtlich langfristiger Infektfreiheit gelegt hat.

Im Hinblick auf die klinische Signifikanz dieser Thematik wären jedoch weitere, insbesondere prospektiv angelegte Studien wünschenswert.

Introduction

Total knee- and hip arthroplasty (TKA, THA) are considered to be successful treatment strategies for end-stage osteoarthritis of the knee- and hip joint regarding both pain relief and functional improvement. In recent years, a steady rise of patients undergoing TKA and THA could be observed, probably due to higher functional demands in order to provide an active lifestyle despite of advanced arthritis of the affected joint or age [1, 2]. Therefore, the expectancy on survival of new prosthetic designs is becoming greater continually [3]. Actually, the continuous innovation and improvement of implants have led to an increased implant-survival and decreased implant-wear. The occurrence of periprosthetic joint infections (PJI), however, has not decreased with those developments. Rather the contrary, the constantly increasing number of joint replacements is accompanied by a rising number of cases that evolve with infection as well [4, 5]. With a reported incidence of less than one percent after primary hip- and less than two percent after primary knee replacement - and a considerable higher rate after revision surgery - PJI therefore represents one of the leading causes for revision following total joint arthroplasty of the lower extremity [1, 6, 7]. Furthermore, it is a potentially devastating condition, often accompanied by a high level of morbidity and mortality [6, 8].

Therefore, the management of lower-extremity periprosthetic joint infections remains a challenging task, as early diagnosis and adequate treatment strategies seem to be mandatory to avoid irreparable damages of the joint and its surrounding tissue or even systemic complications [1].

Besides radical debridement of periprosthetic tissue without implant removal, surgical treatment options include direct exchange arthroplasty, two-stage revision arthroplasty, resection arthroplasty and arthrodesis [2, 4]. Despite these partly well described methods of infection control, no generalised consensus exists in terms of standardised therapeutic strategies for the management of PJI. Suggested reasons for that are various clinical findings and the absence of prospective randomised trials [9-16].

Although two-stage revision surgery seems to be the procedure of choice especially for late chronic PJI, the results remain unpredictable and hard to standardise, certainly also due to large differences in terms of recommended dates for first- but especially second-stage surgery [15, 17].

Pathogenesis of PJI

The majority of periprosthetic infections occurring within the first year after primary joint replacement are initiated through the introduction of microorganisms at time of surgery. Once they come into contact with the implant, microorganisms colonize its surface. A significant factor in this process is the low inoculum of microorganisms needed to establish infection in the presence of the prosthetic material. This can be explained by the so called biofilm formation [18]. The causing microorganisms are predominantly gram-positive bacteria, such as the Staphylococcus aureus and the Staphylococcus epidermidis [19].
Within biofilms, microorganisms are enclosed in a polymeric matrix and develop into organized, complex communities with structural and functional heterogenity [20]. Even monomicrobial biofilms, especially those that are long-standing, may consist of subpopulations of the same organism with different phenotypic or genotypic characteristics as well. The biofilm growth consists of stages, beginning with the attachment of microbial cells to a surface and the initial growth on the surface, followed by maturation of the biofilm and ultimately, detachment. [18]. In the biofilm, microbes are protected from antimicrobial agents and host immune responses. Therefore, biofilm microorganisms have much greater resistance to antimicrobial killing than do planktonic bacteria [8]. Biofilm formation also explains why some physiological organisms, traditionally considered as harmless, become pathogens when growing in the presence of foreign bodies [4, 18].

Contiguous spread of infection from the adjacent tissue is the second mechanism which may lead to periprosthetic infection. Either postoperative surgical site infections or later occurring traumatic events or surgical procedures of the neighbouring tissue can progress to involve the prosthesis [4, 7, 8, 18].

Finally, the risk of hematogenous seeding of the prosthesis remains throughout a lifetime, even though some pathogens represent a higher risk than others. Staphylococcus aureus for example, is, amongst others like Coagulase-negative staphylococci, Streptococcus species, Enterococcus species, and aerobic Gram-negative bacilli, a frequently isolated pathogen in cases of PJI [21-23]. The most frequent sources of bacteremia are skin, respiratory tract, dental, and urinary tract infections [8].

Patient-related risk factors which are associated with an increased risk of the occurrence of PJI are advanced age, malnutrition, obesity, diabetes mellitus, rheumatic diseases, immuno-compromising diseases, such as HIV-infection or previous infections after arthroplasty or other joint surgeries [7, 19].

Diagnosis of Periprosthetic Joint Infections

Medical History and Physical Examination

Despite the wide range of available tests for diagnosis of PJI, there are the initial history and the physical examination that remain the most crucial. Particular attention should be drawn to every patient presenting with pain after total joint arthroplasty. As a general rule, every patient that presents with a painful total joint replacement should be considered infected until that diagnosis can be effectively ruled out [8, 24].

The first priority is to obtain the clinical history carefully. The presence of any known risk factors, including prior infection, diabetes, smoking, obesity, malnutrition and other medical comorbidities, previous bacteremic events, such as other surgeries or dental work, should be noted. Prolonged time of surgery, excessive wound drainage or wound healing problems, needed blood transfusions, and use of additional antibiotics could be potential risk factors as well [4, 7, 8, 18]. It is also important to know detailed information regarding the quality and quantity of pain including onset, severity and character as well as the presence or absence redness or erythema around the joint [24, 25]. Early infections typically present as an acute joint pain, effusion, erythema and fever [8, 18, 24].

Laboratory Tests

Blood examination, especially inflammatory values, is one of the basic diagnostic procedures in the initial evaluation of a patient with suspected PJI. For these cases, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be obtained first. These tests are known to have a high sensitivity. If either the ESR or the CRP is elevated in a patient with a suspected PJI, aspiration of the joint should be considered next [8, 18, 25].

Serum interleukin 6 (IL-6) is a more recently available marker and promising as more specific for acute infection but not yet available in all laboratories [25].

Multiple studies have investigated the utility of serum white blood cell count (WBC) in diagnosis of PJI [26-29]. The authors concluded that was not as useful as ESR or CRP and is therefore not recommended as a screening method for PJI.

Although the role of procalcitonin was mainly investigated in patients with infections of the respiratory-tract so far, it plays an increasing, although not yet clearly defined, role in the diagnosis of PJI as well [28, 29].

However, it is important to note that the level of these serum markers may be affected by age, sex, and medical comorbidities of the patient [30-32]. It was also described that these markers may be elevated for up to 60 postoperative days [33].

Blood cultures for aerobic and anaerobic organisms should be extracted if the patient shows systemic signs of infection, or if the patient has a suspected concomitant infection [34].

Microbiological Examination

Diagnosis and treatment of PJI, as well as treatment success, are to a large extent dependent on the successful detection and identification of the infection causing pathogen. Microbiological examinations can be performed out of blood cultures, joint aspirations or intraoperative specimens [24, 28, 35, 36]. If ever possible, specimens should be obtained prior to the initiation of antibiotic treatment. Wound swabs of superficial wounds or sinus tract infections should be avoided because they usually reflect the microbial colonization from the surrounding skin [24, 37]. Joint aspiration and differential cells count can be useful for initial diagnosis of PJI [35, 36]. A synovial-fluid leukocyte count of more than $1.7 \times 10^3/mm^3$ or a differential count with more than 65% of neutrophils is considered to be consistent with PJI of the knee-, a leukocyte count of more than $4.2 \times 10^3/mm^3$ or more than 80% neutrophils with PJI of the hip joint [24].

Once PJI is diagnosed and revision-surgery is indicated, it should be imperative to obtain tissue for culture from representative periprosthetic tissue or fluid [33]. To maximize the chance of detecting PJI causing microorganisms, at least three, ideally five to six periprosthetic intraoperative tissue samples or the explanted prosthesis itself should be submitted for aerobic and anaerobic culture at time of surgery [34]. Although synovial or tissue cultures provide a specificity of 95–100 %, they have a sensitivity of just 56–75 % [38, 39]. As a possible cause, infections with biofilm-forming pathogens are suggested. These infections are particularly difficult to culture. Biofilms are able to encapsulate bacteria in a small nidus of infection that can cause inflammation in large areas of tissue because of secreted toxins and inflammatory mediators. If the biopsy misses the small biofilm population among the involved tissue, a false-negative culture will be the result [4, 7, 28, 40]. Further reasons for false-negative results may be previous antimicrobial therapy, low inoculum of microorganism, low number of tissue specimens, inappropriate culture medium, inadequate culture incubation time, or a prolonged transport-time to the laboratory [24].

Histologic examination

Histopathologic examination of the implant surrounding tissue has a specificity of more than 90% as well as a high sensitivity (> 80%) [8]. The definition of acute inflammation in the periprosthetic tissue varies in studies from 1 to 10 or more neutrophils per high-power field at a magnification of 400. Furthermore, the degree of infiltration with inflammatory cells may vary considerably among the different specimens. Therefore, areas with the most florid inflammatory changes should be taken for histologic assessment [28, 41]. Histologic examination and definition of PJI consequently may have a high interobserver variability. Caution should be paid in cases with a suspected elevated neutrophil count, such as periprosthetic fractures or inflammatory arthritis as well [8, 24]. The major disadvantages of histopathologic examinations lay in the lacking possibility of identification of the infection-causing microorganisms on the one hand and the difficulty of interpretation of specimens taken from patients with an underlying inflammatory disease, such as rheumatoid arthritis, on the other hand. [28].

Sonication

Given the fact that some bacteria have the ability to adhere to artificial surfaces, which is called biofilm formation, this may partly explain the relatively high proportion of false negative results from microbiological examinations of joint fluid, gained from joint aspiration, as well as from intraoperatively taken periprosthetic tissue specimens [42].

Using sonication to dislodge microorganisms from the surface of explanted devices significantly increases the sensitivity of culture up to 79 % [7, 28].

Although implant sonication was suggested to be helpful especially in patients who received antimicrobial therapy prior to surgery, a recent study discovered periprosthetic tissue cultures to be less affected by antimicrobial treatment than sonication fluid cultures, regardless of sonication fluid culture being more sensitive than periprosthetic tissue cultures in terms of microorganism detection [7, 28, 43].

Another advantage of sonicate cultures is the more frequent identification of mixed infections compared to periprosthetic tissue cultures [7]. Furthermore, more than one morphologic type of the same organism was frequently found in sonicate cultures, indicating different growth stages of microorganisms within the biofilm formation. However, the relevance of these findings certainly needs further investigations [7, 33].

To conclude, it could be said that although sonication fluid culture provides a faster diagnosis and detects about 30% more pathogens, there are remaining culture-negative cases of PJI. In recent literature, false-negative results were described to be obtained in ten percent of all cases with PJI [43].

Imaging Studies

Plain X-Rays

Plain radiographs should be performed in every patient with a painful total joint replacement, although it's utility for the diagnosis of PJI is limited. Ideally, these radiographs should be compared to prior obtained imaging to evaluate for progressive or new signs of loosening or osteolysis [25]. However, it is usually not possible to distinguish between septic and aseptic loosening based on a radiograph only [19]. In cases of aseptic loosening, a slow and progressive substantial bone resorption can be observed, while early signs of failure such as unexpected bone loss, especially when accompanied by corresponding clinical signs and symptoms, should let one think of the possibility of PJI [25, 44].

Ultrasound

Ultrasonography can be used to guide joint aspiration, especially when joint effusion cannot be clearly established [7]. Furthermore, ultrasound-guided synovial biopsy is described of being a valuable tool for large-scale synovial tissue sampling [45].

Nuclear medicine

Radionuclide studies represent physiologic processes concerning metabolic phases. Radiopharmaceutical incorporation into the bone depends on perfusion and rate of new bone formation. However, 99mTc bone scintigraphy was recognized of not being specific for the diagnosis of PJ [46-50]. Although sensitive, it is not possible to distinguish among the causes of prosthetic failure, especially not specifically PJI. Increased bone remodelling is described to be normally present around the prosthesis during the first postoperative year [7]. In addition, aseptic loosening cannot be differentiated from infection [46].

The method of choice for detection of PJI is therefore suggested to be a bone 99mTc scintigraphy combined with 99mTc-ciprofloxacin scan, with 99mTc-hexamethylpropylene amine oxime (HMPAO) leukocyte scintigraphy, or with 99mTc-labeled antigranulocyte monoclonal antibodies [48, 49]. The pooled sensitivity and specificity of the anti-granulocyte scintigraphy with 99mTc-labeled monoclonal antibodies for the diagnosis of PJI were 83% and 79%, as described in a recent meta-analysis. The authors therefore concluded that this diagnostic procedure still has a reasonable role in the diagnosis of PJI after total joint arthroplasty [50].
The role of fluorine-18-fluorodeoxyglucose positron emission tomography (PET) for differentiation of infection and aseptic loosening in total hip arthroplasty is still discussed controversely, probably due do great variations in described specificity (9-83%) and sensitivity (28-100%) [7].

Sectioning procedures

Although the routinely use of computed tomography (CT) and magnetic resonance imaging (MRI) is not recommended by the AAOS Clinical Practice guidelines for diagnosis of PJI, these imaging procedures do surely have the advantage of accurate representation of sinus tracts, soft tissue abscesses, bone erosion and periprosthetic lucency, although metallic artefacts may reduce image quality. This may be one of the reasons for these procedures staying limited in the diagnosis of PJI [7, 51, 52].

Despite the large number of available diagnostics, the definition of PJI remains controversial [25]. The diagnosis of PJI can be challenging as no “gold standard” for diagnosis exists. Most of the available tests do not evaluate PJI specifically but infection in general [25, 40].

Definition of Periprosthetic Joint Infections

Based on the Musculoskeletal Infection Society (MSIS) criteria, PJI is definite if at least three of the following criteria are met [53]:

(1) There is a sinus tract communicating with the prosthesis; or

(2) A pathogen is isolated by culture from at least two separate tissue or fluid samples obtained from the affected prosthetic joint; or

(3) Four of the following six criteria exist:

(a) Elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration

(b) Elevated synovial leukocyte count

(c) Elevated synovial neutrophil percentage

(d) Presence of purulence in the affected joint

(e) Isolation of a microorganism in one culture of periprosthetic tissue or fluid, or

(f) Greater than five neutrophils per high-power field in five high-power fields, observed from histologic analysis of periprosthetic tissue at 9400 magnification.

PJI may be present if fewer than four of these criteria are met.

Classification of Periprosthetic Joint Infections

Early, delayed and chronic infection

According to the classifications of Fitzgerald Jr. (1977) and Schafroth et al. (2003), infections associated with prosthetic joints can be classified as early, occurring within 3 months after surgery, delayed, occurring between three and 24 months after surgery, and late, more than 24 months after surgery, infection [37, 54]. More current guidelines of the American Academy of Orthopaedic Surgeons (AAOS), the Infection Disease Society of America (IDSA) and the International Consensus on PJI, do distinguish between early and late infections as well, however, an early infection is considered to occur only within three weeks of arthroplasty [52, 63, 71]. Early and delayed infections are usually acquired during implantation of the prosthesis, whereas late infections do predominantly occur due to haematogenous seeding [8, 37].

The risk of PJI is considered to be the highest during the first two years after implantation, with a persisting, but lower level risk later on [24].

Early infections are most often accompanied with S. aureus, S. epidermidis and gram-negative bacilli as infection causing agents. Early, as well as delayed infections are both considered to be of nosocomial origin, which do arise from microorganisms found on the natural skin flora, with the difference of less virulent organisms, such as Coagulase-negative Staphylococci or Propionibacterium acnes, causing delayed manifestations [7, 56]. The causing agents of late infections are mostly of community origin and are determined by the apparent source of bacteria, for example anaerobic bacteria causing dental infections while skin infections are often associated with S. aureus or streptococci [19].

Early infections are typically associated with a sudden onset of symptoms such as joint pain, effusion, erythema and warmth of the affected side, whereas delayed infection usually present subtle signs and symptoms, such as implant loosening and persistent joint pain and may therefore be difficult to distinguish from aseptic failure [7]. PJI does not only reflect an infection of the prosthetic interface, but also an infection of the surrounding bone and soft tissues [55].

McPherson et al. developed a staging system for periprosthetic hip infections that categorizes not only the type of infection but also the systemic medical health status and the local wound condition [57].

The systemic host status is graded as A (uncompromised), B (compromised), or C (significant compromise), corresponding to a number of factors, including the presence of neutropenia, low CD4 T-cell count, or age of over 80 years. The local status is graded as 1 (uncompromised), 2 (compromised), or 3 (significantly compromised), corresponding to the presence of local chronic active infection, soft tissue loss, or the presence of a fistula or subcutaneous abscess, among other factors [18], (Table 1).

The classification of each infection may assist the surgeon identify the severity of each infection case and choose an appropriate treatment option [58].

Infection Type	Systemic Host Grade	Local Extremity Grade
I: early postoperative infection (< 4 postoperative weeks)	**A: uncompromised**	**1: uncompromised**
II: hematogenous infection (duration < 4 weeks)	**B: compromised** (1-2 compromising factors)	**2: compromised** (1-2 compromising factors)
III: late chronic infection (duration > 4 weeks)	**C: significant compromise** (> 2 compromising factors) or one of • absolute neutrophil count < 1000 • CD4 T cell count < 100 • intravenous drug abuse • chronic active infection at another site • dysplasia or neoplasm of the immune system Compromising factors: • age > 80 • immunosuppressive drugs • alcoholism • malignancy • chronic active dermatitis or cellulites • pulmonary insufficiency chronic indwelling catheter • renal failure requiring dialysis • chronic malnutrition • systemic inflammatory disease • current nicotin use • systemic immune compromise • diabetes • hepatic insufficiency	**3: significant compromise** (> 2 compromising factors) Compromising factors: • active dermatitis or cellulites • subcutaneous abscess > 8 cm²

Table 1: Classification of infection developed by McPherson et al. in 1999, consisting of acuteness of infection, overall medical and immune health status and local wound condition

Acute and chronic infection

Two classification systems are most often used to determine whether there is an acute or chronic case of PJI. Tsukayama et al. divided the occurrence of infection into four groups: positive intra-operative cultures (at time of implantation of the prosthesis), early postoperative infection (< 4 weeks), late chronic- (> 4 weeks, indolent onset), and acute hematogenous infection (acute onset) [59, 60].
The other commonly used classification, proposed by Zimmerli et al, defines the PJIs as early (occurring within 3 months postoperatively), delayed (3-24 months) and late (> 24 months) [8, 59].
Table 2 summarises the classification of prosthetic joint infection, as defined by Zimmerli et al., according to the route of infection and the time of symptom onset after implantation [8].

Classification	Characteristics
According to the route of infection	
Perioperative	inoculation of microorganisms into the surgical wound during surgery or immediately thereafter
Haematogenous	through blood or lymph spread from a distant focus of infection
Contiguous	contiguous spread from an adjacent focus of infection (eg, penetrating trauma, pre-existing osteomyelitis, skin and soft tissue lesions)
According to the onset of symptoms after implantation	
Early infection (<3 months)	predominantly acquired during implant surgery or the following 2 to 4 days and caused by highly virulent organisms (eg, Staphylococcus aureus or gram-negative bacilli)
Delayed or low-grade infection (3–24 months)	predominantly acquired during implant surgery and caused by less virulent organisms (eg, coagulase-negative staphylococci or Propionibacterium acnes)
Late infection (>24 months)	predominantly caused by haematogenous seeding from remote infections

Table 2: Classification of infection as described by Zimmerli et al., according to the route of infection and the time of symptom onset [8]

Treatment

General Principles

Effective treatment of PJI requires a combination of surgical intervention and suitable antibiotic therapy in most of the cases. Accordingly, the best outcome can be achieved through a multidisciplinary collaboration involving orthopaedic surgeons, microbiologists and infectious disease physicians [18, 61].
Treatment strategies aim primarily infection control and subsequent eradication. Later on, treatment strategies should focus on the restoration of function and the minimizing of infection-related morbidity and mortality.
Options for management include implant-retention without surgery, débridement and implant-retention (with or without long-term suppressive antimicrobial treatment), implant removal without replacement (Girdlestone-hip), arthrodesis (knee) and the one- or two stage implant-exchange [8]. The goal of surgery must be the entire removal of all infected tissue and implants to remove the biofilm and ensure the efficacy of the postoperative antibiotic therapy.
The systemic therapy, however, should not be initiated before multiple intraoperative specimens are sent for microbiological analysis, unless the patient shows signs of a systemic infection/sepsis [8, 18].
Depending on type and design of different studies analysing the outcome following various therapeutic strategies for PJI, the treatment success has been variably defined in the literature over the last three decades as well. One definition of treatment success following arthroplasty exchange has recently been defined as microbiological and clinical eradication of the infection without relapsed infection, freedom from subsequent surgical intervention for the same infection, and freedom from mortality related to the PJI. This definition of treatment-success following PJI was proposed by an expert panel [18, 55, 62].

No Surgery

In some patients, especially those with severe co-morbidities who have an increased operative risk, a curative treatment in the sense of implant removal and appropriate surgical debridement of the infected tissue may not be possible.

These patients may be best managed conservatively, either by long-term antibiotic suppression or acceptance or even the new creation of a chronically discharging sinus [8, 61].

Debridement with Prosthesis Retention

The so called DAIR procedure (**D**ebridement, **A**ntibiotics and **I**mplant **R**emoval) includes the sampling of periprosthetic tissue within the setting of periprosthetic debridement and removal of all infected and necrotic tissue, followed by the exchange of all modular components [34, 63, 64]. This procedure should be performed by the use of an extended approach (open arthrotomy) since debridement must be thorough and complete and the joint needs to be irrigated extensively to ensure the eradication of PJI.
Postoperatively, after collection of tissue samples for microbiological examination, a broad-spectrum therapy is typically consulted, since the causative microorganisms are not detected yet. After detection of the infection causing pathogen, the antimicrobial therapy can be modified. Recent guidelines from the Infectious Diseases Society of America (IDSA) suggest 4 to 6 weeks of intravenous therapy in cases of PJI due to other organisms other than staphylococci or when the rifampicin combination therapy cannot be used [63]. Due to the possibility to achieve high intracellular levels and its ability to penetrate biofilms, rifampicin is the medication of choice for treatment of PJI caused by staphylococcus species [65].
Clinical practice guidelines from the IDSA suggest the DAIR procedure for patients with well-fixed implants without a sinus tract and a recent onset of symptoms (< three weeks) respectively early PJI (occurring within four weeks after joint arthroplasty) [8, 65].
However, the reported success rates for DAIR vary widely (14–100 %) [8, 66-68].

One-Stage Exchange

Although the two-stage revision arthroplasty has been widely accepted as the treatment of choice especially for late chronic infections, there is no evidence of higher success compared to the one-stage exchange arthroplasty in current literature [55]. As a matter of fact, the one-stage implant exchange has some undeniable advantages compared to all more-stage procedures: The reduced number of surgeries is accompanied by reduced hospitalization times and reduced relative overall costs [8, 55].

The surgical technique includes the radical debridement of periprosthetic tissue with all nonbleeding tissues and related bone to be radically excised. Tissue samples are taken from all relevant areas of the operation site for microbiologic and histologic evaluation [69]. Afterwards, all implants, including the bone cement, are removed completely and a new prosthesis is implanted and usually fixed by the use of antibiotic-loaded bone cement (Figure 1).

The kind of antibiotic augmentation of PMMA is either determined by the pathogen identified preoperatively or empirical if the infection-causing pathogen could not be detected yet [18].

Although the indications for one-stage exchange arthroplasty for PJI are not clearly defined, there do exist some recommendations in the literature. Typically, the procedure is used only for patients with hip arthroplasty infection [18]. According to the suggestions of Gehrke et al., the most essential and relevant pre-operative diagnostic tool is the joint aspiration for the purpose of precise identification of micro-organisms [55]. Almost all authors describe the need of an identified pathogen preoperatively, which should be susceptible to antimicrobials available orally and in PMMA. A further relative requirement for one-stage exchange is the presence of an adequate bone stock and good conditioned surrounding soft tissue [34, 63, 70]. Contraindications for one-stage exchange arthroplasty include the failure of previous periprosthetic infections treated with one-stage procedures, infected nerve–vessel bundle, unknown preoperative pathogen specification, the non-availability of appropriate antibiotics and the presence of a sinus tract, which is usually associated with a late chronic infection [69, 71].

Systemic antimicrobial therapy is assessed following performance of an

antibiogram of detected organisms for a period of 10 days to 6 weeks postoperatively, followed by an oral follow-on therapy [8, 68, 69].
The two-stage approach, as the most reported procedure for the management of PJI, has a reported reinfection rate between 9 and 20% [55, 68, 72].
Currently, although there are some studies that support a one-stage exchange as a reasonable alternative for treating an acute postoperative infection, the best treatment for acute postoperative infection after THA remains to be determined [73-76]. The reported success rates for this procedure vary between 75% and 90%, depending on the length of follow up [68, 69, 77, 78].

Two-Stage Exchange

The procedure of two-stage revision for treatment of prosthetic joint infections is considered to be the most definitive strategy in terms of eradication of the infection, especially for treatment of late chronic infections [18]. Investigating the current literature and guidelines for the treatment of PJI, a larger number of articles focussing on the two-staged exchange can be found. This procedure has become a benchmark for treatment recommendations, including also numerous proposals concerning the duration of antibiotic treatment, the use of static or mobile spacers and the interval of spacer retention. However, these recommendations are mostly based on opinions and low-evidence studies rather than on prospective, randomised data [55, 78].

The procedure involves a two staged arthroplasty-exchange with a time period of some weeks in between. The first stage includes the removal of all components and PMMA, followed by the radical debridement of all infected or necrotic soft tissue and nonviable bone in order to remove all potential sources of infection [79]. Then, an antibiotic-loaded cement coated joint spacer is implanted into the joint space instead of definite implants (Figure 2). This spacer acts as a slow release system of antibiotics to ensure a high local concentration released to the surrounding tissue [72, 79]. The spacer can be either static, with the joint being immobilized, or articulating, with the aim to maintain the range of motion and patients' mobility until second-stage surgery.

A few studies have reported on the superiority of articulating- over static spacers in terms of infect eradication in prosthetic infections of knees and hips [80-88]. However, despite of advantages like a facilitated re-implantation and better functional results, it seems to be still unclear whether the efficacy of infection control is comparable between articulating and static spacers.

Once the first-stage surgery is completed, with obtained tissue samples in a sufficient number for microbiologic and histologic evaluation and the removed implants prepared for sonication, the intravenous antibiotic therapy can be induced.
Usually, the duration of intravenous therapy ranges from 2 to 6 weeks, followed by 2 to 4 weeks of antibiotic withdrawal, in order to avoid distorting the results of pre-

operative microbiological examinations (joint aspirations) [80].
The second-stage surgery is undertaken when there is evidence of cured infection. To monitor the success of treatment, inflammatory laboratory values of CRP should be obtained regularly between stages to ensure the antibiotics used are effective [80, 86]. With laboratory values steadily normalizing, repeated negative joint aspirations and inconspicuous clinical signs and symptoms infection is supposed to be eradicated.
The second stage involves the removal of the spacer and further debridement to healthy tissue, if required, by the use of the previous approach. Multiple periprosthetic tissue-specimens are taken for further microbiological analysis and femur and tibia are prepared for (revision-) arthroplasty [79]. If there is evidence of ongoing infection, a repeat debridement procedure may be performed, typically followed by further antimicrobial therapy before attempted reimplantation [18].
If the periprosthetic tissue seems unremarkable and the frozen-section examination is negative, the revision arthroplasty can be performed. The new implants may be fixed either uncemented or cemented and with- or without the use of additional antibiotics for PMMA-augmentation (Figure 3).

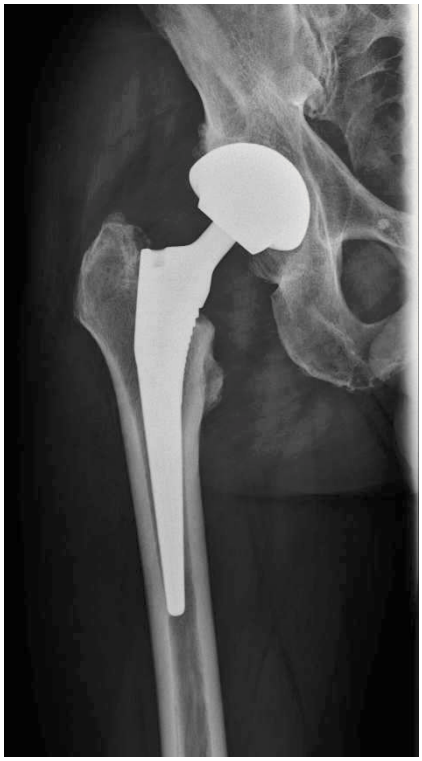

Fig.1 a

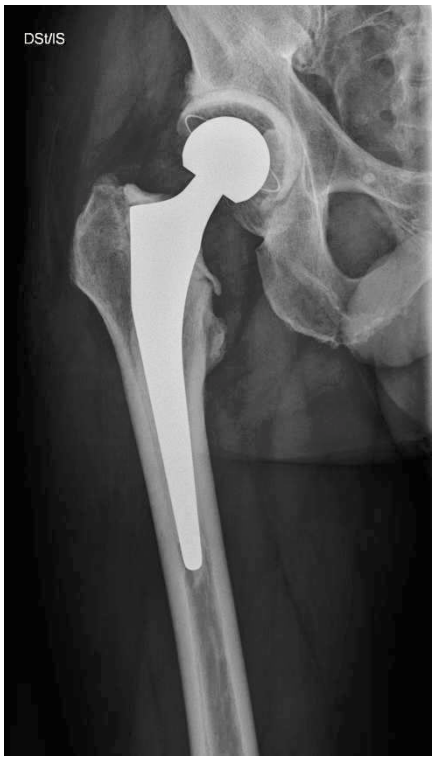

Fig. 1b

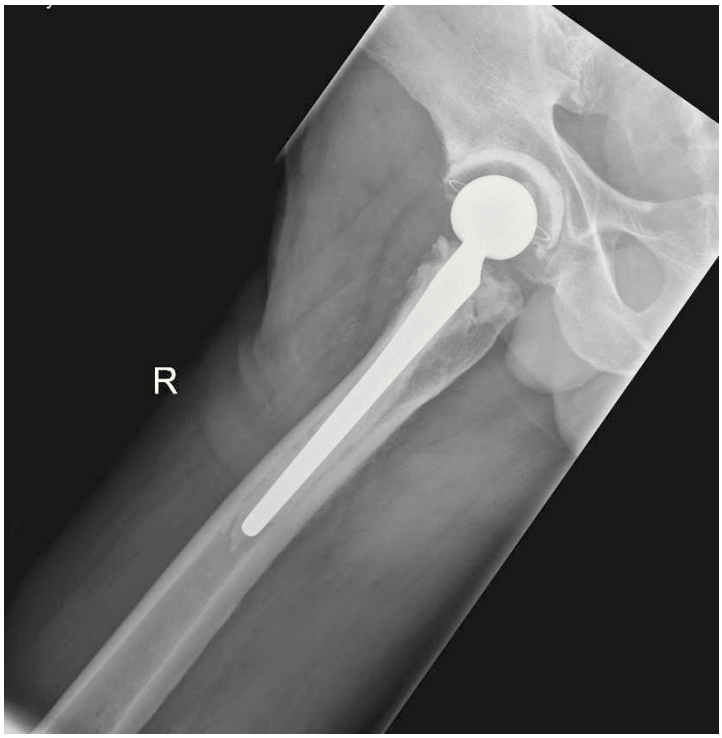

Fig. 1c

Fig.1a-c: Plain antero-posterior and axial radiographs of a 67-year-old female after One-Stage Exchange Arthroplasty for periprosthetic hip joint infection

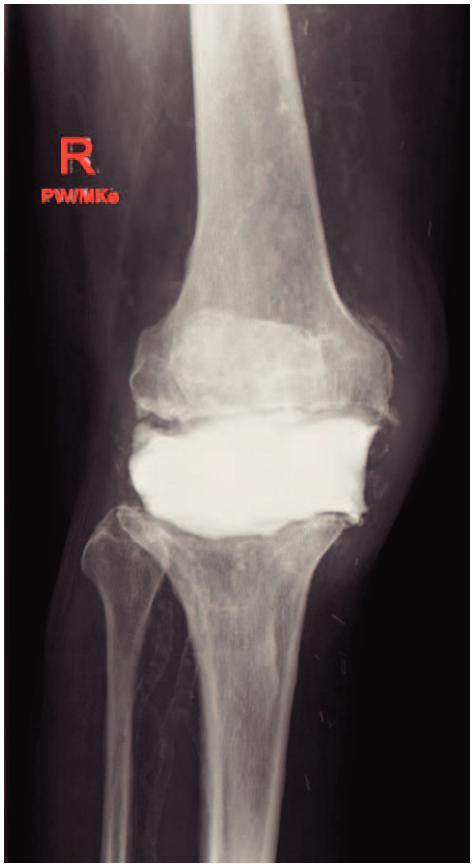

Fig. 2a

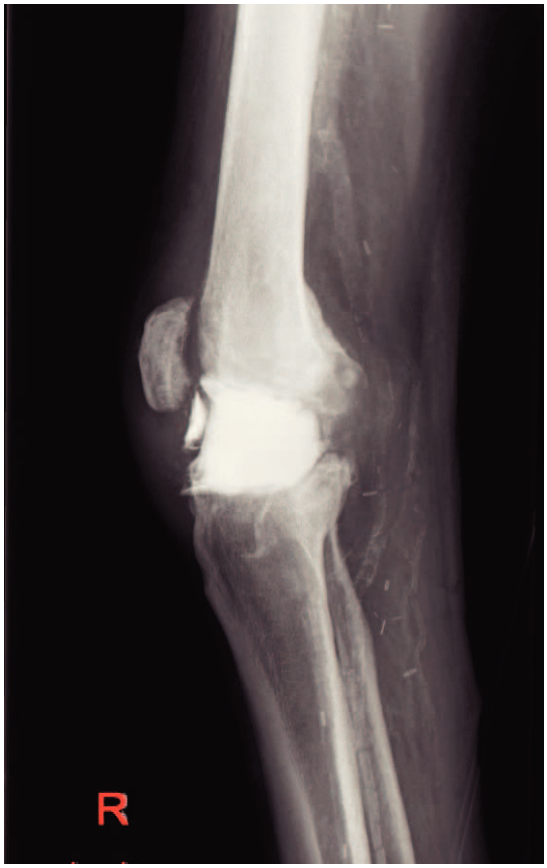

Fig. 2b

Fig. 2a, b: Plain antero-posterior and lateral radiographs of a 75-year-old male patient with periprosthetic knee joint infection after Implant-Removal and Spacer-Implantation

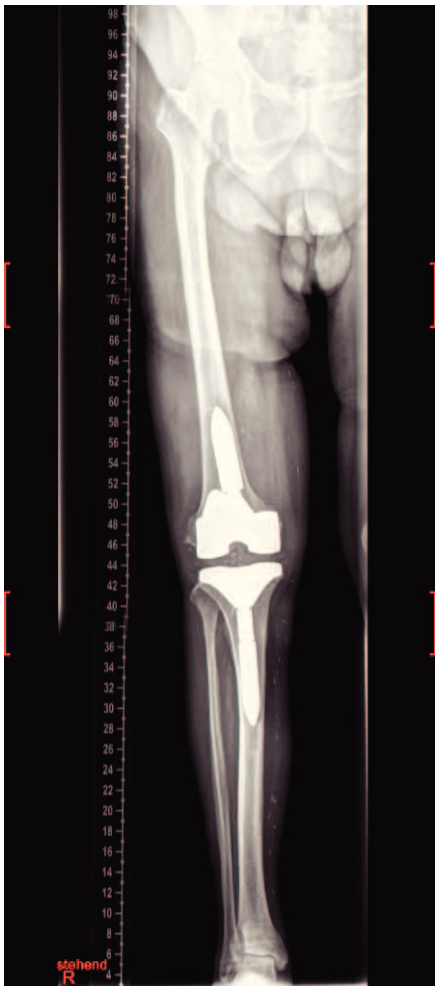

Fig. 3a

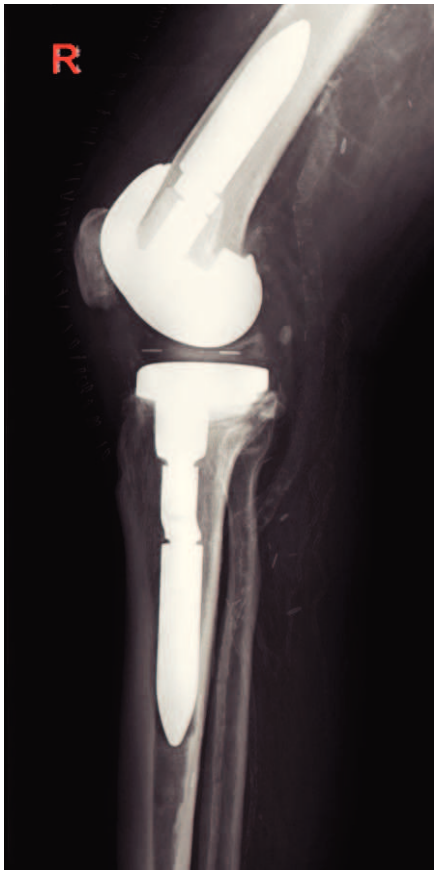

Fig. 3b

Fig. 3a, b: Plain antero-posterior and lateral radiographs of the same patient after Second-Stage Surgery

Following successful replantation, there is no further need for a systemic, long-term antibiotic therapy [79].
As mentioned above, the success rates for the two-staged procedure range from 74.5% to 100% with an average success rate of 90% [55, 68, 72, 78, 80].

Resection arthroplasty and arthrodesis

Although prosthetic joint reconstruction after infection is possible in the majority of cases, occasionally cases of several, unsuccessful attempts of joint reconstruction after PJI do occur, mostly due to massive bone loss or poor local conditions. Alternatively, patients with other comorbidities that limit their functional abilities and patients with a poor general condition may elect to undergo a one-stage salvage procedure as well [80]. One possible procedure may be a resection arthroplasty, within the meaning of joint removal without replacement [18]. This so called Girdlestone procedure (hip) results in a high rate of infection control and also pain relief according to literature [90, 91]. However, within the light of our experiences, we cannot confirm the pain relief in patients who have undergone a resection arthroplasty of the hip joint for PJI.
Furthermore, all patients show significant limb length discrepancies, resulting in massive shortening of the muscles. These circumstances may complicate a potential later implemented revision arthroplasty essentially.
Arthrodesis may be performed in patients following resection of a knee arthroplasty, in order to provide additional mechanical support to permit ambulation [18, 18, 28].
For patients with bad local conditions and/or difficult-to-treat wound healing problems, amputation may be the best option to prevent further complications [80].

Please see Figure 4 for a graphic depiction of the treatment algorithm as used at our institution.

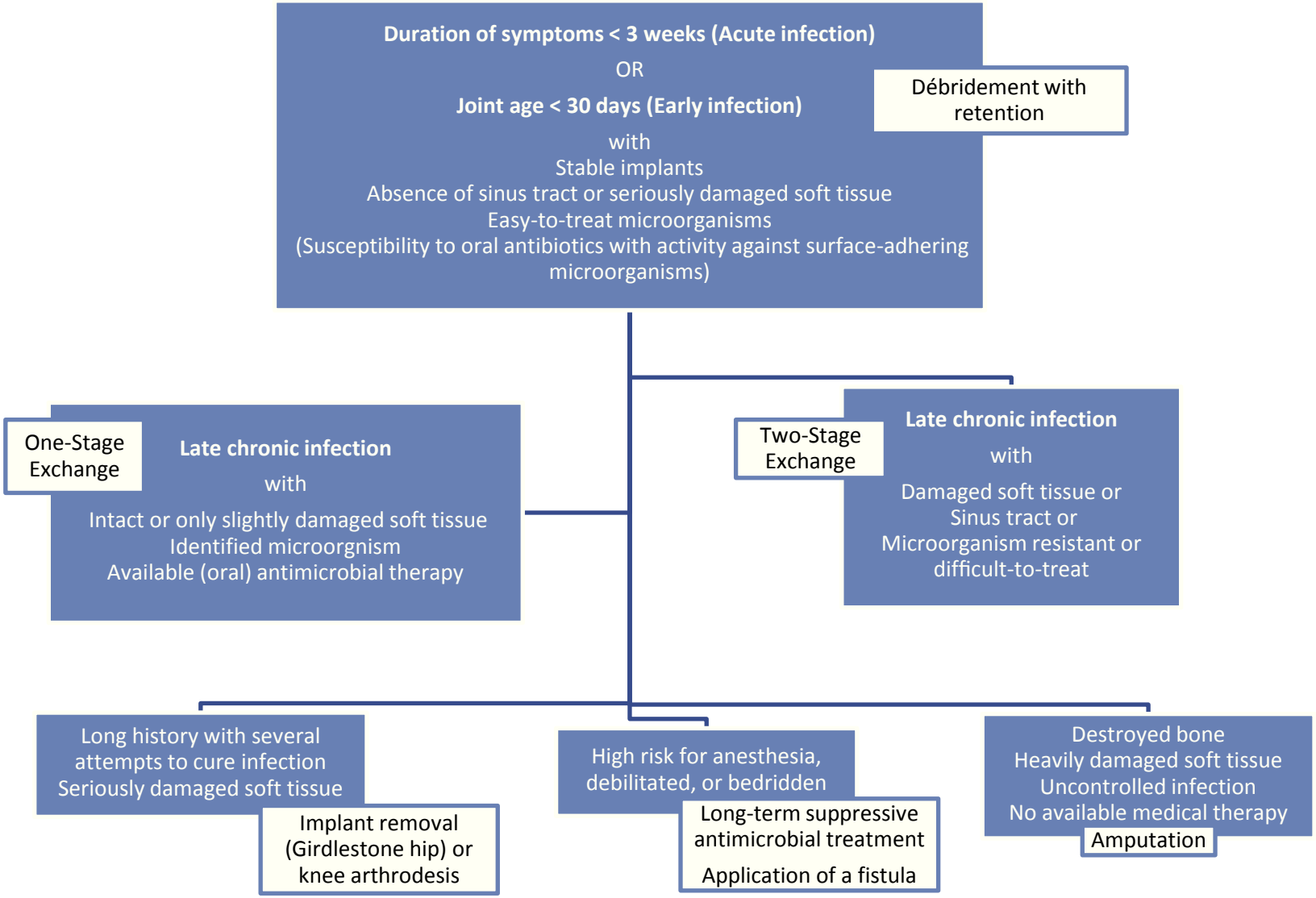

Fig. 4: Treatment algorithm for PJI according to classification, systemic- and local conditions

Two-stage revision of prosthetic hip- and knee joint infections using antibiotic-loaded cement spacers: When is the best time to perform the second stage?

Aim of the Study

Two-stage exchange arthroplasty, as described above in the section “Treatment”, seems to be the procedure of choice, especially for late chronic infections. Nevertheless, the results following a two-stage revision remain unpredictable, certainly not just because of specific circumstances of the individual cases (resistant or difficult to treat microorganisms, local- and general conditions etc.), but also due to large differences regarding the recommended treatment protocols [4-10]. One such example would be the time period between first- and second-stage procedure, thus the joint-spacer retention-period. To our knowledge, there do not exist any recommendations for its optimal duration [4, 8, 12, 15, 17].
We hypothesized, that the length of the spacer-retention period plays an essential role with regard to a durable eradication of infection.
In order to determine the best time for second-stage arthroplasty, the data of all patients who have undergone two-stage exchange arthroplasty for prosthetic hip- and knee joint infections between 2005 and 2010, respectively 2004 and 2013, were analyzed statistically in terms of (1) mortality rate and (2) reinfection rates in dependency of the duration of spacer-retention. Furthermore, we determined (3) outcome differences with regard to various causing microorganisms and individual parameters (sex, age, BMI).

Patients and Methods

Between 2004 and 2013, a consecutive series of 76 patients diagnosed with prosthetic hip joint infections, as well as 77 patients diagnosed with prosthetic knee joint infections, were included into the study. All of these patients have undergone two-stage revision arthroplasty by the use of antibiotic-loaded cement spacers.

The patients with PJI of the hip consisted of 38 men and 38 women with an average age of 66.5 years (range, 20.3-87.2 years). The mean body mass index of the patients was 26.1 (range, 15.2-39.3). The right hip was affected in 46 cases, the left hip in 30 cases. Seven patients had to be excluded before the data analysis was performed. Four were lost to follow-up, three did not satisfy our diagnostic criteria mostly due to diagnosis and (pre-) treatment in another institution prior to referral to our department.
Of the total 88 patients treated for PJI of the knee joint in the investigated period, ten did not satisfy the diagnostic criteria and one patient failed to appear for any follow-up examination. Eventually, the data of 35 men and 42 women with a mean age of 64.9 years (range, 31.3-82.4 years) was consulted for final analysis. The right knee was affected in 37 cases, the left knee in 40 cases. The average observation period was 100 months (range, 6- 277 months).

Diagnosis

Patient's history and clinical findings were assessed with regard to previous interventions, symptom duration, antibiotic treatments and general and local comorbidities. Inflammation indices (complete blood count with total and differential leukocyte count, C-reactive protein, fibrinogen and interleukine 6) as well as blood cultures in cases of fever or other systemic signs of infection were obtained. Preoperative joint aspiration for long-term incubation was performed in each case prior to first-stage surgery and initiation of antimicrobial therapy, if possible. Further bacteriological examinations were carried out during/after first-stage surgery (frozen sections, intraoperative cultures, sonication for more recent cases). Standardised radiographs (complete leg, knee in two planes, patella tangential; pelvis, hip in two planes) were taken and compared to previous radiographs, if available, to assess signs of loosening.
In cases of inconclusive clinical, laboratory or bacteriological findings (low-grade infections), a 99mTc-leukocyte scintigraphy was performed additionally.

Infection was diagnosed according to the criteria of the Musculoskeletal Infection Society (MSIS). Classification of infection was performed according to the staging

system developed by McPherson et al. in 1999, consisting of assessment of the acuteness of infection, the overall medical- and immune health status and the local wound condition [5, 6].

Surgical technique

First-stage procedure

The first-stage procedure included the collection of periprosthetic specimens (synovia, synovial fluid, joint capsule) for frozen sections and cultural examination, followed by the removal of all prosthetic components, including the PMMA and the radical debridement of infected tissue and bone surfaces.
Surgical procedures were performed through a lateral approach (Bauer's approach; hip), respectively a median parapatellar approach (knee). In cases of prosthetic hip joint infections, we used a cemented femoral stem and a metal head, coated with antibiotic loaded cement as a temporary joint spacer. This construct has the shape of unipolar hemi-arthroplasty. Optionally, a cemented polyethylene cup was implanted as well. The size of the spacer was selected intra-operatively according to the size of acetabulum respectively the extent of the bony defect. For knee joint infections, antibiotic loaded bone cement was inserted as a temporary joint spacer. The antibiotic loading of the PMMA was performed either empiric or according to the sensitivity of the antibiogram. Most of the spacers were augmented with one gram of vancomycin per 40 grams of PMMA.
Redon-drain removal was performed on the fifth postoperative day, after collecting tissue samples for cultural examination as well as for the determination of local vancomycin levels (for more recent cases).
Patients were mobilized with touch-down weight bearing by the use of two crutches, a long-leg cast was applied additionally for all cases with prosthetic knee joint infections.

Interim period (Spacer retention-period)

The interim period included 4-8 weeks of systemic antibiotic therapy. A prolonged interval of 6 to eight weeks is described to be useful for infections with difficult-to-treat microorganisms such as methicillin-resistant S. aureus or other multidrug resistant bacteria [8]. Initially, antibiotics were applied intravenously. An oral therapy was administered after release from hospital. The antimicrobial treatment was initiated in collaboration with an experienced infectiologist, either empiric or in cases of positive cultural examinations according to the pathogen-specific antibiogram. Culture-negative patients with a silent history concerning PJI were treated with vancomycin. Anyway, antimicrobial therapy was discontinued two weeks before second-stage surgery (reimplantation) in order to obtain reliable tissue specimens for culture at the time of surgery. Furthermore, repeated joint aspirations (at least two times) were performed to rule out a persisting infection following first-stage surgery. If the intraoperatively obtained specimens showed no signs of active inflammation or microbial growth, no further antibiotic therapy was applied. For other cases, the therapy was reinitiated for further three months.

Second-stage Procedure

Infection was considered to be eradicated with the resolution of clinical signs and symptoms, negative repeat aspiration for three times, the improvement of laboratory infection values and a negative 99mTc-leucocyte scintigraphy. If those criteria were met, the second stage operation, including spacer removal, collection of periprosthetic tissue samples for frozen section and cultures once again, debridement and lavage, were performed. The further procedure was depending on the intra-operative findings (frozen section, local status), either the replacement of the temporary joint spacer or revision arthroplasty or, in cases of worse local conditions, knee arthrodesis.

All included patients were followed up half-yearly for at least two years after second stage surgery to determine the long-term outcome regarding re-infection rates.

Postoperative care

The primary goal of the follow-up care was the early detection of re-infection. These follow-up examinations included physical examinations, laboratory tests (complete blood count, C-reactive protein and fibrinogen) as well as imaging procedures including plain radiographs of the hip in two planes and, in case of inconclusive clinical and laboratory findings, additional bacteriological examinations (joint aspiration) and a 99mTc-leukocyte scintigraphy.

Statistical analysis

Data were entered into a computerized database and analyzed. Continuous variables are reported as Median with interquartile range (IQR) or range (minimum-maximum) except for age and BMI which are described with the mean with the standard deviation (SD). Categorical data are displayed as frequencies with percentages in parentheses.

To determine the optimal spacer retention period, we used the ‘maximally selected rank statistic" method, calculated with the R-package “maxstat” [92, 93]. To determine the statistical significance of group differences the Wilcoxon rank-sum test was performed.

Cross tabulations (Chi-Square test, two tailed Fisher’s exact test) were used to assess the relationship between categorical variables. In either case exact p-values were calculated which were considered as statistically significant if equal or less than 0.05. All computations were done using the statistical package IBM SPSS Statistics (Release 19.0.0. 2010. Armonk (NY), USA: International Business Machines Corporation).

Results

Pre-operative diagnostics and assessment

Clinical manifestations ranged from reduced mobility, impaired range of motion, pain, swelling and/or redness of the affected region to systemic signs of inflammation or even sepsis. The main clinical symptoms were pain, joint swelling and effusion, overheating and movement restriction of the affected joint.
The mean time period between primary joint arthroplasty and onset of the symptoms was 92 months (range, 2-252 months) for hips and 47 months (range, 2.4-336 months) for knees (Figure 5).

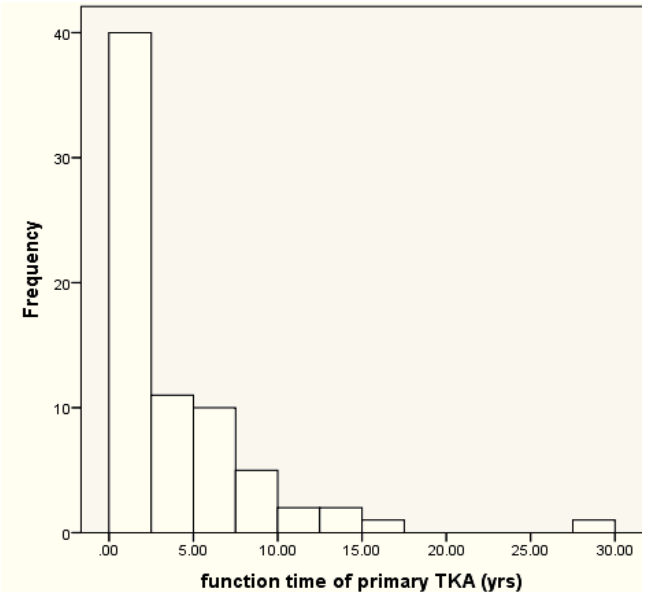

Figure 5: Function time (=time to infection) of TKA's in years

Pre-operative laboratory inflammation parameters were elevated in most of the patients. In cases of prosthetic knee joint infections, the pre-operative laboratory inflammation parameters were elevated in most of the patients.

The mean preoperative C-reactive protein concentration was 89.0 mg/l (IQR 91.55 mg/l; range, 3.3-331.7), the mean leucocyte count was 14000 /µL (IQR 5820; range, 2680-34940 /µL), the mean fibrinogen- 595.7 mg/dl (range, 210-1100 mg/dl) and the mean IL-6 concentration was 68.1 pg/dl (range, 2-334 pg/dl).
For hip joint infections, we observed the following values: The mean preoperative C-reactive protein concentration was 30.2 mg/l (IQR 65.0 mg/l; range, 3.2-337), with a mean leucocyte count of 7710 /µL (IQR 2680; range, 3600-21890 /µL).

Pre-operative joint-aspirations were performed in all patients. An organism could be detected either in the pre-operative, or both the pre- and intra-operative taken samples in 50 cases (65.8%) for hip- and in 54 cases (70.2 %) for knee joint infections. In 16.9% of the knee-patients, the detection of infection-causing microorganisms succeeded exclusively through the method of sonication. The most common identified organisms were staphylococci, followed by streptococci, gram negative rods and mixed cultures of organisms (Table 3a and b).
Unfortunately, the method of sonication was not commonly used a few years earlier, when most of the patients with PJI, as presented in this study, were treated at our department.
In 34.2% respectively 29.8% of the patients, the infection-causing germ could not be identified, neither by preoperative performed joint aspiration, nor by intraoperative obtained tissue or sonication.
Significantly higher pre-operative CRP-values could be observed in cases with detected microorganisms than in those without microbial detection (median 46.6 mg/L [IQR 84.4] and 15.3 mg/L [IQR 21.0], $p<0.001$) (Figure 6).

Detected microorganisms from joint-aspirations and intraoperative obtained tissue	n	%
Not identified	26	34.2
Staphylococci	24	31.6
Streptococci	8	10.5
Gram negative rods	6	7.9
2 Staph subgroups	2	2.6
Strep/Staph	2	2.6
3 Gram neg. Rods subgroups/Strept	1	1.3
2 Staph subgroups/Strep	1	1.3
2 Staph subgroups/gram neg. Rods	1	1.3
Gram neg. Rods/Strep	1	1.3
Gram neg. Rods/Staph	2	2.6
Others	2	2.6

Table 3a: Causing microorganisms in cases of PJI of the hip (cultured out of tissue samples or joint aspiration samples taken either pre-operatively or both pre- and intra-operatively during first-stage surgery)

Detected microorganisms from joint-aspirations and intraoperative obtained tissue	n	%
E. faecalis	3	3.9
E. faecium	1	1.3
E. faecium, E. faecalis	1	1.3
Group C streptococci	1	1.3
Group G streptococci	1	1.3
MRSA	1	1.3
P. aeruginosa	2	2.6
P. aeruginosa, Bacillus cereus	1	1.3
Pseudomonas aeruginosa, Finegoldia magna	1	1.3
S. aureus	13	16.9
S. aureus, E. faecalis	1	1.3
S. capitis	3	3.9
S. epidermidis	8	10.4
S. hominis	1	1.3
S. hominis, E. faecalis	1	1.3
S. hominis, S. haemolyticus	1	1.3
S. lugdunensis	1	1.3
Detected microorganisms from Sonication	n	%
P. acnes	1	1.3
P. aeruginosa	1	1.3
S. aureus	4	5.2
S. capitis	2	2.6
S. epidermidis	5	6.5

Table 3b: Causing microorganisms (PJI of the knee)

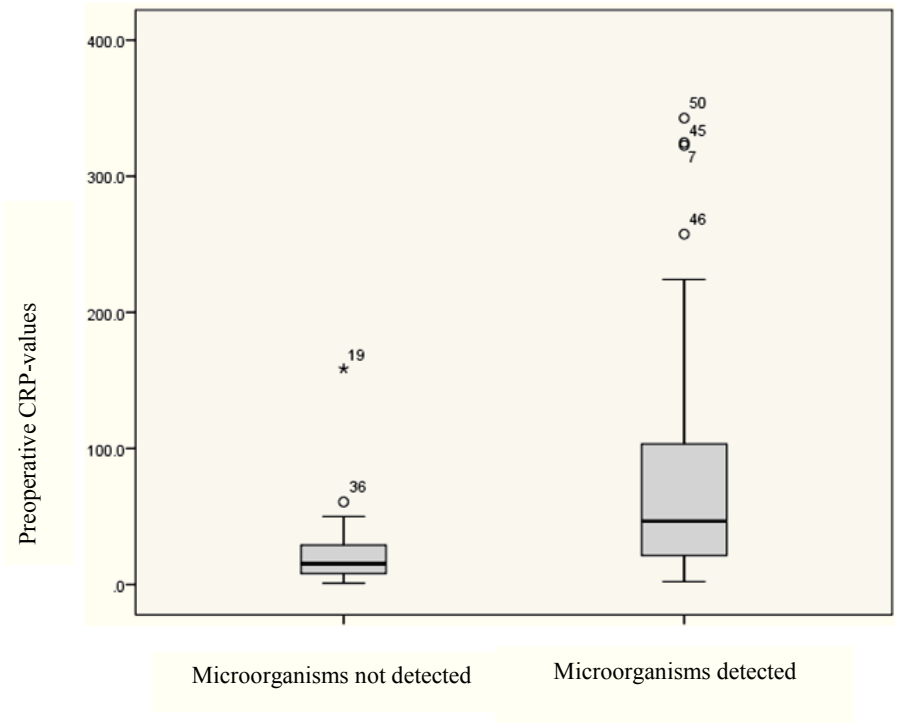

Fig.6: Correlation between successful detection of infection-causing microorganisms and pre-operative (first-stage) CRP-values in the investigated series

Patients with detected microorganisms have shown significantly higher pre-operative CRP-values than patients without detected microorganisms (median 46.6 vs 15.3 mg/l; $p<0.001$)

Classification of PJI

According to the classification system of McPherson et al., 14 cases (9.2%) were classified as early postoperative infections, 15 patients (9.8%) suffered from haematogenous infection. The great majority of 151 patients were diagnosed with late chronic infections (81%). More detailed information regarding both local and systemic host grades are presented in Table 4a and b.

McPherson	n	%
I A 2	1	1.3
I B 1	3	3.9
I B 2	4	5.2
II B 1	2	2.6
II B 2	10	13.0
II C 2	3	3.9
III B 1	9	11.7
III B 2	17	22.1
III B 3	5	6.5
III C 2	14	18.2
III C 3	9	11.7
Total	77	100

Table 4a: Type of infection according to the classification of McPherson et al. in patients with PJI of the knee

McPherson	n	%
I A 2	1	1.3
I B 1	3	3.6
I B 2	2	2.6
III A 1	11	14.5
III A 2	11	14.5
III A 3	1	1.3
III B 1	4	5.3
III B 2	28	36.8
III B 3	5	6.6
III C 1	2	2.6
III C 2	6	7.9
III C 3	2	2.6
Total	76	100

Table 4b: Type of infection according to the classification of McPherson et al. in patients with PJI of the hip

First stage surgery and spacer period

All of the included patients have undergone first-stage surgery as explained above, including the insertion of an antibiotic-augmented cement-spacer for knee-, respectively a cement-coated joint-spacer for prosthetic hip infections. We therefore used PMMA with gentamicin (PALACOS Bone Cement, Zimmer, Switzerland). Additional antibiotic loading was performed either empiric or according to the antibiogram.
According to that, we used vancomycin in 145 (94.8%) of the cases. Piperacillin/tazobactam was applied in four (2.6%), vancomycin/refobacin in two (1.3%)- and teicoplanin and cefuroxime in one case each (1.3%).

After first-stage surgery, all patients were evaluated continuously in terms of clinical and laboratory improvements. Leucocyte-scintigraphy was performed within the first two weeks after completion of systemic antibiotic therapy in most of the patients. Interestingly, however, in 57 out of 123 cases (46.3%), false-positive results were provided. In order to exclude risks in accordance with persisting- or reinfection, at least three repeated joint aspirations were performed before second-stage surgery.
Four patients have died within the interim-period due to poor general conditions (all of them were classified as IIIC3 infections according to McPherson et al.) and therefore have not undergone second-stage surgery.

The median overall spacer retention-period was 12.6 weeks (range, 0.6 to 91.3 weeks) for hip- and 10.6 weeks (IQR 8.0 weeks) for prosthetic knee joint infections.

Second stage surgery

One additional spacer exchange was necessary in 13 cases of prosthetic hip joint infections due to positive signs of acute infection in the frozen section and suspect intra-operative findings. 8 patients have not been operated for a second time in the investigated time period due to poor general conditions. All remaining patients have undergone second-stage surgery (cemented revision arthroplasty).

Within the group of patients with knee infections, one additional spacer exchange was necessary in 15 (19.7%), two exchanges were performed in 2 patients (2.6%) due to persisting signs and symptoms of infection. All patients have undergone the second-stage. 73 patients received a revision semi- or constrained knee arthroplasty. In two patients, knee-arthrodesis via arthrodesis nail was performed due to a destroyed extensor system (quadriceps tendon and patella). Occurring complications after completition of the second-stage were a severe arthrofibrosis in one case, treated by capsulotomy and arthrolysis, a persistant fistula in one case and a periprosthetic femoral fracture, treated with distal femoral replacement.

Prosthetic hip joint infections: Outcome

Reinfection rate

After a mean follow-up of 20.5 months (range, 0-78 months) after second-stage surgery, reinfection has not occurred in 53 patients (69.7%). In 23 of the patients (30.3%), PJI has re-occurred, 2 of them (2.6%) have died within 6 weeks after spacer implantation for systemic manifestation of infection.

Spacer-retention period

To determine the optimal spacer retention period, we used the ‘maximally selected rank statistic" method, calculated with the R-package “maxstat” [92, 93].
For PJI of the hip, the logrank test revealed two maxima, one at 28 and one at 77 days. Therefore, the optimum spacer retention-period was estimated as 4-11 weeks. To determine the statistical significance of group differences the Wilcoxon rank-sum test was performed. In 40 patients, we observed a spacer retention-period of 4-11 weeks, 5 patients had a spacer retention-period of less than 4 weeks and 23 patients of more than 11 weeks. We observed a significantly higher proportion of patients free from reinfection until final follow up in the 4-11-week group (90.0%; p-value: 0.014) (Figure 7).
The worst outcome was observed for shorter spacer retention periods as well as for prolonged spacer retention periods (<11 weeks), which have leaded to a re-infection rate of 47.8%

Individual parameters

No significant influence on the outcome regarding re-infection rates could be determined for the preoperative body mass index (BMI) or patients’ age or gender.

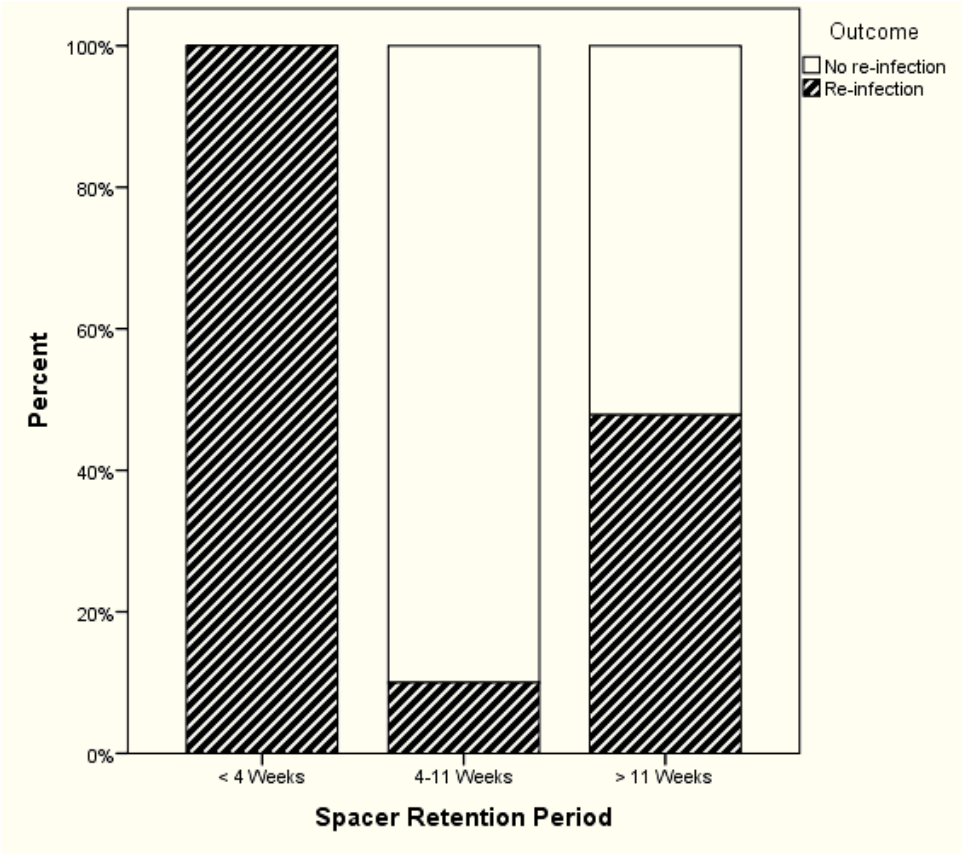

Fig. 7: Reinfection rates for patients who have undergone two-stage revision arthroplasty, dependent on spacer-retention periods

Prosthetic knee joint infections: Outcome

Reinfection rate

After a mean overall follow-up time of 35 months (range, 6-108 months) reinfection has not occurred in 61 patients (81.3%). In 14 of the patients (18.7%), PJI has reoccurred. In seven of these patients (9.1%), another two-stage procedure, including revision arthroplasty, was performed. Transfemoral amputation was necessary in two patients, due to worse local and general conditions. One patient has died within the spacer-retention period. The remaining four patients have undergone knee arthrodesis.

Spacer-retention period

To determine the optimal spacer retention period, we used the ‘maximally selected rank statistic" method, calculated with the R-package “maxstat” [92, 93]. This method which calculates the cut-point that maximizes the logrank test statistic yielded a maximum at 83 days for knee joint infections. Thus, the optimum spacer retention-period could be estimated as less than 12 weeks.

In 14 patients, PJI has reoccurred following one completed two-stage revision procedure after a mean time of 99 days (range, 1-278 weeks). For these patients, the median length of spacer-retention was 15 weeks (IQR 8.9 weeks) within the first, and 13 weeks (IQR 7.9 weeks) within a repeated (=second) two-stage procedure.
Therefore, it could be proven that a prolonged spacer-retention period (>83 days) does lead to a significant higher proportion of reinfections (p=0.016) (Figure 8).

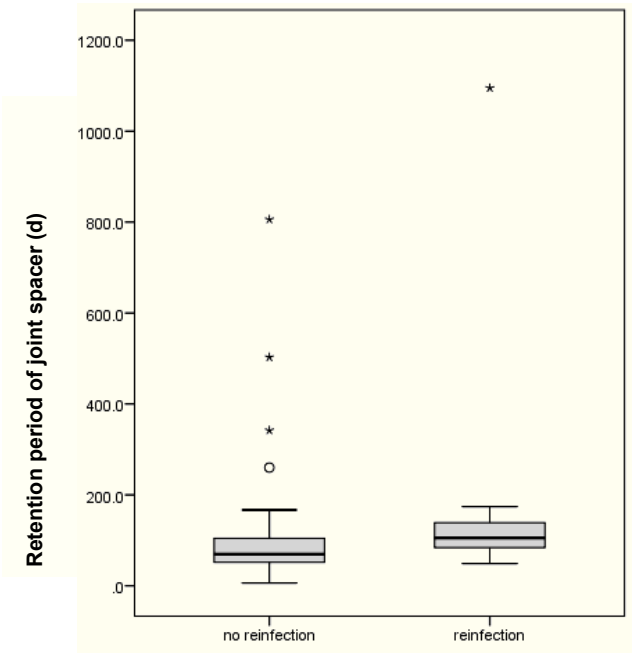

Fig.8: Correlation between spacer-retention (days) and outcome (reinfection)

Individual parameters

Significant compromising local conditions of the periprosthetic tissue and surrounding skin have influenced the outcome negatively. 6 out of 12 patients, who were classified as Grade 3 with regard to the local extremity grade (classification according to McPherson et al.) suffered from reinfection following two-stage revision surgery for PJI of the knee (42.9% of the overall reinfection rate). This was statistically significant (p=0.005) (Table 5).
No significant influence on the outcome regarding re-infection rates could be determined for the preoperative imflammatory markers, patients' age or gender.

		no Reinfection		Reinfection		Total	
		n	%	n	%	n	%
Local extremity	1 (uncompromised)	14	23.0%			14	18.7%
grade	2 (compromised)	41	67.2%	8	57.1%	49	65.3%
	3 (significant compromised)	6	9.8%	6	42.9%	12	16.0%

Table 5: Reinfection rates in patients who have undergone two-stage revision for PJI arthroplasty depending on the local extremity grades

A further negative predictor was the number of performed spacer-exchanges between first- and second-stage procedure. 6 (66.6%) out of 9 patients with one additional spacer-exchange suffered from reinfection following completed two-stage procedure. The worst outcome could be observed in patients who have undergone spacer-exchange arthroplasty twice (n=2) (p=0.001). Infection has reoccurred in both of these cases (p=0.001) (Table 6).

		No reinfection		Reinfection		Total	
		n	%	n	%	n	%
Number of	**Total**	**61**	**100.0%**	**14**	**100.0%**	**75**	**100.0%**
Spacer	1	51	85.0%	6	42.9%	57	77.0%
exchanges	2	9	15.0%	6	42.9%	15	20.3%
	3			2	14.3%	2	2.7%
	Total*	60	100.0%	14	100.0%	74	100.0%

Table 6: Reinfection rates in patients who have undergone two-stage revision for PJI arthroplasty depending on the number of performed spacer-exchanges

Discussion

Although diagnosis and treatment of infection have improved during the past decade, the management of periprosthetic joint infections remains a challenging task due to multifaceted clinical presentations and manifestations, the absence of uniform criteria for the diagnosis of infection associated with prosthetic joints and the lack of data from randomized, controlled trials [4-10, 94].

Although the new criteria for diagnosis of PJI, as proposed by the MSIS committee, solved the lack of standard definition for PJI, there is still no single "gold standard" test for diagnosis of PJI [95]. In our investigated series, infection was diagnosed according to the criteria of the Musculoskeletal Infection Society (MSIS) as well. Classification of infection was performed according to the staging system developed by McPherson et al. in 1999, consisting of assessment of the acuteness of infection, the overall medical- and immune health status and the local wound condition [5, 6].

In our studies, infection was diagnosed according to the recent classification of the Musculoskeletal Infection Society (MSIS) [14]. In cases of inconclusive clinical, laboratory or bacteriological findings, a 99mTc-leukocyte scintigraphy was performed additionally. However, our data has shown that this nuclear medicine examination method, although very helpful for the primary diagnosis of PJI, it does not seem suitable to confirm the eradication of infection in patients, who have already undergone implant removal and several weeks of antimicrobial therapy in order to undergo second-stage surgery [46, 47, 50]. Quite the contrary, leucocyte-scintigraphy provided false-positive results in almost half of the patients.
Effective treatment of PJI requires a combination of surgical intervention and suitable antibiotic therapy in most of the cases [36, 61]. Accordingly, the best outcome can be achieved through a multidisciplinary collaboration between orthopaedic surgeons, microbiologists and infectious disease physicians [18, 61]. Although the primarily aim of treatment is certainly the control of infection and its' subsequent eradication, the further goal should be the restoration of function and the minimizing of infection-related morbidity and mortality [18, 55]. Unfortunately, this is not possible for all of patients suffering from PJI. Surgical treatment options,

although often required, may not be possible or appropriate in some of the cases as well. Especially in patients with severe co-morbidities and a resulting increased operative risk, a curative surgical treatment may not be possible. These patients may be best managed conservatively, either by long-term antibiotic suppression or acceptance or even the new creation of a chronically discharging sinus [8, 61].

Further options for the management of PJI, especially suitable for patients with an increased operative risk as well as for long-term immobilised patients, include the débridement and implant-retention, the so called DAIR procedure (with or without long-term suppressive antimicrobial treatment), implant removal without replacement (Girdlestone-hip) or arthrodesis (knee) [4-10, 18, 28].
The procedure of one-stage exchange arthroplasty for early or acute infection respectively the two-stage revision surgery for delayed prosthetic joint infections are considered to be the most definitive strategies in terms of infection eradication [8, 34, 55, 63, 69-73, 76, 79-80].
Despite of all these partly well described methods of infection control, no generalised consensus exists regarding standardised therapeutic strategies for the management of PJI [2–10]. Although two-stage exchange arthroplasty seems to be the procedure of choice especially for late, chronic infections, the results remain unpredictable and hard to standardize due of large differences regarding the detailed treatment protocol, for example the recommended time period between first- and second-stage surgery [4-10, 15, 17].
In our series, all patients have undergone two-stage exchange arthroplasty by the use of antibiotic-augmented cement spacers. This technique is well described and associated with success rates of 70 to 90% [8, 96-98]. One suggested reason for treatment failure is a persisting infection, often with the same causing organisms [99, 100]. Another reason for persisting infection following two-stage treatment could be the high incidence of false-negative results of pre- and intraoperative obtained tissue samples, with regard to the infection-causing microorganisms. If the biopsy misses the small biofilm population among the involved tissue, a false-negative culture will be the result [40].
Joint spacers, as they were used to bridge the time between implant removal and replantation, may act as a scaffold for biofilm formation as well [99, 101, 102]. Therefore, the use of antibiotic loaded bone cement for this technique is, even

though suggested, still discussed controversially in current literature, certainly also due to the lack of data from randomized, controlled trials [8, 94, 96, 98, 103]. Especially when a multidrug-resistant microorganism was isolated, the preferred treatment is either external fixation or stabilization instead of the use of an antibiotic impregnated joint-spacer [8, 37].

Further reasons for false-negative microbiological results are primarily foregoing antimicrobial therapy, followed by errors during sampling and processing of the specimens. [24, 104-106].

A reason for renew infection could be attributed to the fact that most of the patients with PJI have undergone complex, prolonged surgery, which is known to be associated with higher infection rates than primary joint replacement [106, 107].

In our series, we observed reinfection rates between ten and almost thirty percent following two-stage revision of PJI. These numbers are consistent with the current literature, the high probability of having false-negative results was recently as reported by Huang et al. as well [103-105].

Therefore, the goal of surgery must be the entire removal of all infected tissue and implants to remove the biofilm and ensure the efficacy of the postoperative antibiotic therapy [8, 18]. In our studies, we defined treatment success as freedom from signs or symptoms of infection after the end of treatment. In literature, however, treatment success has been defined variably depending on type and design of different studies analysing the outcome following various therapeutic strategies for PJI. Recently, treatment success was proposed by an expert panel as the microbiological and clinical eradication of infection without relapsed infection, freedom from subsequent surgical intervention for the same infection, and freedom from mortality related to the PJI [18, 62, 102, 103].

Although the use of cemented implants seemed to be inevitable for revision joint arthroplasty for a long period due to various reasons, as the possibility of adding additional antibiotics to the cement as well as to ensure a stable anchoring of the implants, several recent reports described outcomes comparable to cemented implants by the use of two-stage revision surgery using cementless components [86, 107-109]. In our series, we used cemented implants exclusively. We decided on this procedure due to our experience of lost bone stock and thinned-out, especially femoral corticalis following cured hip joint-infections, cemented implants

are used for both primary- and revision knee arthroplasty as well at our institution [6].

Despite the intensive research undertaken on this topic, it seemed not possible to establish a general accepted protocol for the surgical management of periprosthetic joint infections, especially regarding the appropriate timing for revision surgery following implant removal and spacer implantation.

In our series, we achieved the significantly best outcome regarding infection-control in patients who have undergone second-stage surgery four to eleven weeks after first-stage surgery for periprosthetic hip joint infections respectively within 12 weeks for PJI of the knee. Up to 90% of these patients stayed free from infection until final follow-up. An increased number of performed spacer-exchanges, as well as a bad local extremity grade, seemed to have a negative impact on the outcome.
Furthermore, it must be considered that in cases of PJI, standard antimicrobial-susceptibility tests cannot be used to reliably predict the outcome. Ideally, the antimicrobial agent should have bactericidal activity against surface-adhering, slow-growing, and biofilm-producing microorganisms. Therefore, the presence of difficult-to-treat germs as well as undetected infection-causing microorganisms may therefore influence the effect of the antimicrobial treatment negatively [8, 20, 110-112].

The major strength of this study is that it is, to our knowledge, one of the first focusing on the length of spacer retention and its potential impact on the outcome within the setting of two-stage revision arthroplasty for PJI. These findings may also have advantages for patients treated for PJI at our department in the present and future, since we try to apply our findings regarding the estimated optimal duration of spacer duration.
Our study does also have several limitations, most notably the retrospective study design. This offers the opportunity of several kinds of bias, the first one to note is selection bias. The decision of treatment was always determined by senior surgeons, well experienced in primary and revision joint arthroplasty. Furthermore, all cases were discussed collaboratively and in consideration of the current

literature before the final treatment protocol was determined. Therefore, we believe that we kept selection bias to a minimum.

Conclusion

Although the two-stage exchange arthroplasty seems to be the procedure of choice, especially for delayed and chronic prosthetic joint infections, no consensus exists regarding the length of spacer-retention.
In our investigated series, the optimal time for second-stage procedure ranged between four and eleven weeks for hip joint infections and less than 12 weeks for PJI of the knee.
We believe that patients with PJI of the hip- and knee joint will benefit from our findings, prospective studies to verify the influence of spacer-retention in patients who have undergone two-stage revision are already in progress.
To our knowledge, this study is the first focusing on the length of spacer retention and its potential impact on the outcome within the setting of stage revision arthroplasty for PJI. Nonetheless, given the clinical significance and the expected increase of PJI in the nearer future, further, essentially prospective studies would be desirable.

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