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DISSERTATION

Analysis of the epidemiology and therapy of periprosthetic joint infections of total hip- and knee arthroplasty. A retro- and prospective study on „Klinikum im Friedrichshain, Berlin“ 2010 - 2015

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von

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Zusammenfassung

Ziel der Studie ist es, den Therapieerfolg bei periprothetischen Infektionen von Hüft- und Knie-Totalendoprothesen im untersuchten Patientengut zu erheben und die beeinflussende Faktoren zu identifizieren.

Von 2010 bis 2015 wurden in der Klinik für Orthopädie des Klinikums im Friedrichshain (Berlin) 104 Patienten mit einer Infektion von 61 Hüft- und 43 Kniegelenkstotalendoprothesen therapiert und in die retrospektive Studie eingeschlossen. Die entsprechenden Patientenakten wurden bezüglich Anamnese, klinischer Befunde sowie erfolgter operativer und antibiotischer Therapie ausgewertet. Zusätzlich erfolgte prospektiv eine schriftliche Nachbefragung über den weiteren Krankheitsverlauf sowie das funktionelle Ergebnis mittels des WOMAC Scores. Eine univariate statistische Auswertung sowie die Berechnung der Überlebenswahrscheinlichkeit der unterschiedlichen Patientengruppen mittels Kaplan-Meier-Schätzer wurde durchgeführt.

Ein zweizeitiger Wechsel mit 12-wöchigen endoprothesenfreiem Intervall und dualer Antibiotikatherapie wurde in der Mehrheit der Fälle (95 Patienten) durchgeführt. Im Kniegelenk wurde stets ein Knochenzement-Platzhalter eingebracht. Bei infiziertem Hüftgelenk wurde teilweise mit (23 Patienten) und teilweise ohne Platzhalter (31 Patienten) therapiert. Die durchschnittliche Nachbeobachtungszeit betrug 25,1 Monate. Durchschnittlich waren die Patienten 74 Jahre alt. Die Mehrzahl der Infekte (65%;68 Patienten) wurde als chronisch gewertet mit einer durchschnittlichen Dauer von 65,9 Monaten zwischen letztem aseptischen Eingriff und Beginn der Symptome der Infektion. In den untersuchten Proben wurden hauptsächlich koagulasenegative Staphylokokken (38%) bzw. *Staphylococcus aureus* (15%) isoliert.

Präoperativ durchgeführte Punktionen erbrachten in 32% der Fälle widersprüchliche mikrobiologische Befunde im Vergleich zu den intraoperativen Probenentnahmen; präoperative Biopsien in 39% der Fälle. In 12% der Fälle erfolgte keine Reimplantation. 6% der Patienten verstarb vor Beendigung der Therapie. In 79% der erfolgten Reimplantationen waren im Anschluss keine erneuten Anzeichen einer Infektion aufgetreten. Diesbezüglich zeigte sich kein Unterschied zwischen Knie- oder Hüfttotalendoprothesen. Die Nutzung eines temporären Platzhalters (Spacers) war mit einer verbesserten Kontrolle der Infektion verbunden, jedoch erreichte dieser Effekt keine statistische Signifikanz. Patienten, welche mit biofilmaktiven Antibiotika therapiert wurden, erfuhren keinen signifikant besseren Therapieverlauf. In der Patientengruppe mit einer akut postoperativen Infektion (12 Patienten) zeigte sich nach erfolgter Reimplantation eine größere Rate an notwendigen operativen Revisionen (50%) als in der Gruppe mit einer akut hämatogenen (15 Patienten; Revisionsrate 13%) oder chronischen Infektion (59 Patienten; Revisionsrate 17%). Zum Zeitpunkt der Nachbefragung nahmen 76% der Patienten keine oder Nicht-Opioid Analgetika ein.

Die Therapie einer periprothetischen Infektion des Hüft- und Kniegelenks ist hochkomplex und derzeit mit einer hohen Rate von Rezidiven einhergehend, welche nicht zufriedenstellend erscheint. Die Verwendung eines antibiotikabeladenen Knochenzementspacer scheint zu bevorzugen zu sein. Die Rolle biofilmaktiver Antibiotika und deren Einfluss auf den Behandlungserfolg muss weiter erforscht werden.

Abstract

Aim of the study was to investigate the outcome on periprosthetic joint infections of hip- and knee-arthroplasties and the influence of the treatment in the analysed patient population.

Overall, 104 patients with infection of 61 hip and 43 knee arthroplasties treated between 2010 to 2015 in the orthopaedic department of the „Klinikum im Friedrichshain“ (Berlin) were analysed. Patient charts were reviewed retrospectively. A prospective follow-up survey on the further therapeutic process and the functional outcome by means of the WOMAC Score was performed. Data was evaluated by a univariate statistical analysis and the Kaplan-Meier survival method was used to estimate the probability of infection-free survival of different subgroups.

In 91% (95 patients) a two-staged exchange with 12-week implant-free interval combined with dual-antibiotics was performed. An antibiotic loaded bone-cement spacer has been used continuously in infected knee-arthroplasties. 23 cases of infected hip arthroplaties were treated with and 31 cases without spacer. The mean follow-up period was 25.1 months. The mean age was 74 years. Pathogenesis was presumed to be chronic in 65% (68 patients). The mean period between last aseptic surgical procedure and onset of symptoms was 65,9 months. Mainly coagulase-negative staphylococci (38%) and *Staphylococcus aureus* (15%) were identified in the analysed samples. Compared to the results of intraoperative collected tissue, preoperatively performed joint aspirations yielded in 32% of cases contradictory microbiological findings and preoperative biopsies in 39% of cases.

In 12% of cases no reimplantation was performed; in 6% patients deceased before end of therapy. In 79% of performed reimplantation surgeries, no signs of infection occurred until last follow-up. Regarding outcome, no difference between knee and hip arthroplasties was found, but in hip arthroplasties the use of an antibiotic-loaded spacer was linked to a diminished revision-rate, though this effect did not reach statistical significance. Biofilm-active antibiotics (27 patients) showed no improved outcome compared to other antibiotics (63 patients). In acute postoperative infections (12 patients), a higher rate of necessary surgical revisions (50%) than in acute hematogenous (15 patients; revision rate 13%) or chronic infections (59 patients; revision rate 17%) was found. At time of follow-up, 76% of respondents took either no or non-opioid analgesics only.

In summary, the therapy of periprosthetic joint infections is highly complex and accompanied by an unsatisfactory high recurrence rate. The use of an antibiotic-loaded spacer seems to be preferable. The role of biofilm-active antibiotics and their impact on the treatment outcome must be further investigated.

1 Introduction

In the present study, periprosthetic joint infections of total knee and hip arthroplasties are analysed. Primary and revision arthroplasty and the respective indications and epidemiology will be described, before septic prosthetic failure is outlined more closely.

1.1 Primary arthroplasty

As periprosthetic joint infections are a consequence of primary arthroplasty, its indication and epidemiology are delineated in the following.

1.1.1 Indication for arthroplasty

The two major disease patterns that are treated by total hip or knee arthroplasty, are, by numbers, osteoarthritis and osteoporotic fractures of the hip. As an example, the proportion of the respective indication of the Swedish hip arthroplasty register 2008 is summarized in Table 1. Additional indications for treatment by arthroplasties are rheumatoid arthritis, idiopathic osteonecrosis of the femoral head, aseptic osteonecrosis, dysplasia, tumour, comminuted acetabular fractures [2] or severe fractures adjacent to the knee [3]. The indication for an endoprosthesis in case of osteoarthrosis is given in case of occurrence of multiple factors. Guidelines for the decision, whether an endoprosthesis is recommendable, commonly base on pain and functional deficits, which are not satisfactory treatable by conservative therapy, alongside with corresponding radiological signs of osteoarthritis [4]. Concerning patients with medial fracture of the femoral neck, the total hip arthroplasty has been found to be a recommendable option of treatment [5].

Table 1 - Frequency of Indications for primary hip arthroplasty 2008 in Sweden. Source: [1]

Indication	Frequency
Primary osteoarthritis	83%
Fracture	10%
Idiopathic femoral head necrosis	3%
Childhood disease	2%
Inflammatory arthritis	2%
Other	1%

1.1.1 Epidemiology of primary arthroplasty

The recent decades brought an increasingly higher life expectancy, alongside declining fertility rates accompanied with a resulting over-ageing of the society in American and European countries. Hence, the number of patients suffering osteoarthritis is also rising, with a peak incidence in the seventh and eighth decade of life [6], as depicted concerning

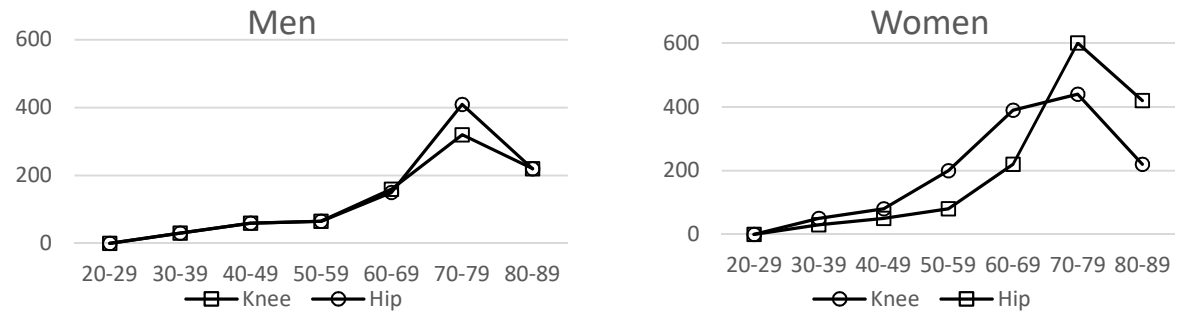
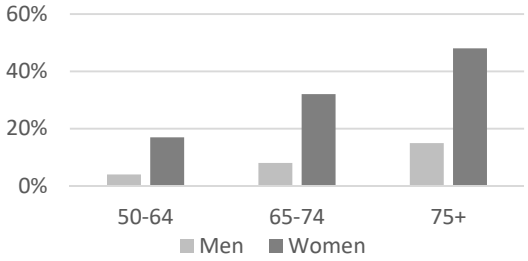


Figure 1 - Incidence of symptomatic osteoarthritis of the knee and hip in relationship to age. Adapted from: [6]

osteoarthritis of knee and hip of the clients of an American insurance in Figure 1. An equal development is to expect regarding osteoporosis, as the prevalence of osteoporosis is also age-dependent with data from the United States and Europe showing a significant increase from the sixth decade of life on.

Showing a prevalence of osteoporosis of the hip around 7% in women aged 50-59 years, it increases up to 22% in the group of women aged 60-69 years [7], as visible in Figure 2. The incidence of femoral neck fracture worldwide is expected to be tripled within the next 50 years [6].

Figure 2 - Prevalence of osteoporosis depending on age and gender in Germany 2009. Adapted from:[7]



As stated above, the number of patients suffering disease patterns being treated by an endoprosthesis is rising. In the year 2011, in Germany an overall of 232.320 of total hip arthroplasties and 168.486 total knee arthroplasties were implanted [8]. Compared to the rest of Europe in the year 2008, the largest number of endoprostheses has been implanted in Germany [9].

More recent OECD-Eurostat statistics from 2013 depicted in Figure 3 show, that this situation changed and in other countries more arthroplasties have been implanted regarding both hip and knee. In 2013, knee replacement surgery has been performed most frequently in Austria and hip replacement most frequently in Switzerland [10].

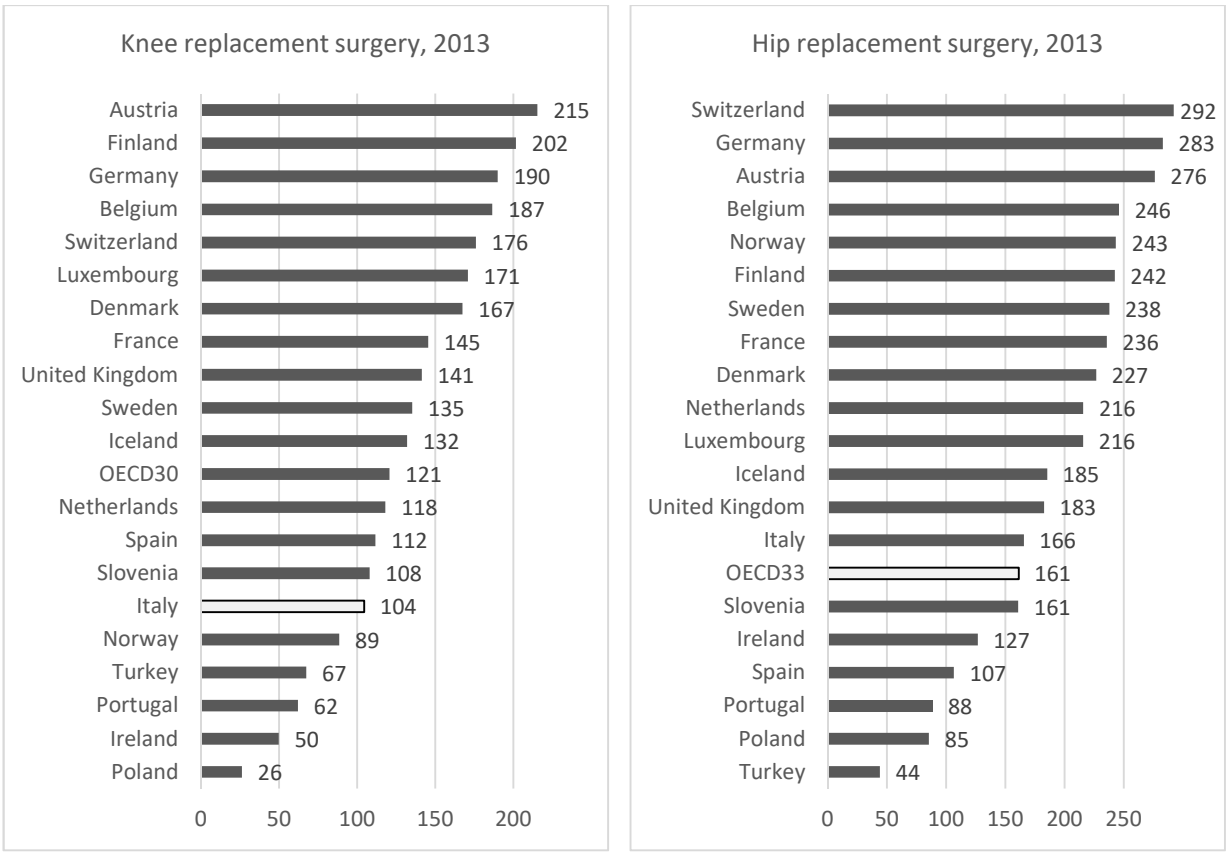


Figure 3 - Knee- and hip replacement surgery per 100 000 inhabitants in selected OECD countries in 2013 (or nearest year). Adapted from: [10]

1.1.2 Cemented and non-cemented endoprostheses

In the past decades, several types of joint replacement have been developed. The way, in which the implants are attached to the bone, is crucial for a long-lasting seating of the endoprosthesis. This can be achieved by either fixating the implant by “bone cement”, consisting of polymethylmethacrylate (PMMA), to the bone or by creating a direct contact between the implant and the bone [11].

Known main advantages of the cemented variant is, that in this way loads can be borne early after operation and in case of a reduced bone density a stable fixation of the implants is achievable. Known drawbacks of bone-cement fixation are embolism and thermal tissue damage [12] and in the long term possible disruption of bone-cement as well as development of osteolysis and granulomatous tissue due to cement-debris [13] with subsequent loosening of the prosthesis [14].

The elasticity modulus of bone cement (3 gigapascal (GPa)) is relatively low compared to cortical bone (10-40 GPa), titanium alloy (110 GPa) or stainless steel (205 GPa) [15].

For prophylaxis and therapy of infections, respectively, low- and high-dose antibiotic-loaded bone cement is available. Against the background of septic disease patterns, the possibility of adding antibiotics to the bone cement is an important option to create a local drug delivery system. In a review of 29 studies, a significantly higher rate for an achieved control of infection in revision surgery with antibiotic-loaded cement (86% vs. 59%) has been found [16].

In case of a non-cemented seating, a direct contact between implant and bone is achieved. To bear full weight, the implant must be integrated into the bone, therefore currently available implants are finished by an osteoconductive coating made of hydroxyapatite. Theoretical advantages of non-cemented arthroplasties are shorter duration of surgery and avoidance of cement-specific complications like embolism and the waiving of thermal tissue damage [12].

Prerequisite for a stable biological integration of the implants into the bony structure is a stable primary stability, which means that relative movements between bone and implant must be diminished. This can be achieved by blocking the implant mechanical within the bone (“press-fit”) or by a screw-mechanism [17,18]. Cemented fixation seems to be superior in terms of outcome and survival-time, especially in elderly patients [19].

1.2 Revision arthroplasty

The occurrence of pathologies, which entail a revision surgery, is always a severe finding. There are several reasons for prosthetic failure, which can be subdivided into aseptic and septic. As the most frequent indication for revision arthroplasty and as main differential diagnosis of septic loosening, the aseptic loosening will be described in first instance.

1.2.1 Epidemiology of revision arthroplasty

First and foremost, the aseptic prosthetic loosening, followed by periprosthetic joint infection with or without loosening are the two most frequent indications for revision-arthroplasties, as shown in Table 2 on the example of the Swedish hip arthroplasty register. The incidence of postoperative infections is reported with up to 2% after primary implantation and from 5% to 20% after revision arthroplasty [20]. The outcome after treatment with in some cases necessary resection arthroplasty, arthrodesis and amputation [21] is not satisfactory given the mainly elective indication for primary joint arthroplasties.

Table 2 - Frequency of indications for revision hip arthroplasty 2008 in Sweden. Source: [1]

Indication	Frequency
Aseptic loosening	50%
Deep infection	17%
Dislocation	15%
Fracture	10%
2-stage procedure	4%
Other	3%

In Germany around 300,000 primary total arthroplasties of the hip and knee are performed per year [8]. Given the percentages mentioned beforehand, this entails between 3,000 to 6,000 periprosthetic joint infections per year. While the risk of suffering a periprosthetic joint infection is increased within the first two years after implantation, a continuous risk remains as long as the prosthesis stays in situ. The risk of an infection of a total hip or knee arthroplasty was found to be 5.9/1.000 “prosthesis-years” in the first two years after implantation and 2.3/1.000 in the following period until the tenth year after implantation [22].

The costs of the therapy of periprosthetic joint infections were found to be with 27,059 € per patient are almost twice the costs of the treatment of an aseptic prosthesis failure, which is 14,760 € per patient [23].

1.2.2 Aseptic loosening

Aseptic loosening is the most frequent indication for revision surgery being caused by a lack of primary stability or an increased abrasion. The occurrence of osteolysis secondary to wear debris is caused by inflammatory mediators being released after incorporation of polyethylene particles or parts of the bone cement by macrophages [24]. This ensues an inflammatory reaction leading to a bone resorption by osteoclasts and development of a granulomatous tissue layer around the implant [25].

While the main symptom of aseptic loosening is pain of the affected joint, it is known, that at the beginning often radiological signs of aseptic loosening are already present in until then symptom-free patients [26]. Since a progressing affection of the bone entails revision surgery of a greater extent, early diagnosis is important. The commonly used primary diagnostic tool is the plain radiography. In a meta-analysis, a specificity of 81% and sensitivity of 82% for loosening of hip stems diagnosed via radiography was found [27]. If aseptic loosening is suspected but cannot be validated by radiography, a 3-phase-sceletal-scintigraphy (technetium-99 m-methylene-diphosphonate-scintigraphy) is another option for diagnosis. Since it proves an increased bone metabolism, a reasonable use is possible after 8-10 month after cemented and 12 months after non-cemented prosthesis implantation, depicting until then the physiological postoperative remodelling processes. In a meta-analysis regarding 3-phase-sceletal scintigraphy, a specificity of 72% and a sensitivity of 85% were found [28]. By combining radiography and scintigraphy the predictive value can be increased [29]. Some authors state, mainly on the results of sonication, that a considerable number of infects stay unidentified and are misinterpreted as aseptic loosening [30].

1.2.3 Septic prosthetic failure – periprosthetic joint infections

As mentioned in chapter 1.2.1 above, septic prosthetic failure is the second leading cause for revision arthroplasty. The infection of a joint replacement has serious consequences for the patient: on the one hand regarding possible complications in the context of a septic disease, on the other hand due to long-term therapy with often multiple surgeries, the immobilisation partially over months and the associated comorbidities.

Risk factors

As patient-dependent risk factors for periprosthetic joint infection inter alia has been identified: rheumatoid arthritis, psoriasis, immunosuppression, steroid therapy, poor nutritional status, obesity, diabetes mellitus and extremely advanced age [31]. Other studies found an increased risk of periprosthetic joint infection patients with an infection of other surgical wounds, a surgical patient NNIS risk score of 1 or 2 (National Nosocomial Infections Surveillance Score), a present malignancy, prior joint arthroplasties [32] hypopotassaemia, hypothyroidism, diverticulosis, venous insufficiency and hypercholesterolemia [33].

Surgery related risk-factors are lack of antibiotic-prophylaxis, lack of antibiotic-containing cement in primary implantation and any postoperative complication [34]. To prevent perioperative infection several techniques like laminar flow in operation theatre and space suits have been developed. A meta-analysis over 51,485 primary total hip arthroplasties and 36,826 total knee arthroplasties observed a reduced risk for perioperative infection for the operations performed in operation theatres equipped with laminar flow in contrast to operations performed in space suits, which showed an increased risk of infection [35].

Pathogenesis of periprosthetic joint infections

In the following section, the pathogenesis of periprosthetic joint infections is described. To date, the understanding of the development of biofilms on indwelling implants is of central importance, which will be described first. Afterwards the different presumed routes of infection will be delineated.

Development of biofilms

Periprosthetic joint infections are frequently caused by bacteria creating a biofilm on surfaces which they adhere to. The biofilm consists of microbial cells and mainly polysaccharide structures, referred to as extracellular polymeric substances, among other materials that depend on the surrounding. Within the biofilm, the bacteria occur in a slow-growing, stationary state, organized in microcolonies [36], being able to interact by release of cell-to-cell signalling modules ("quorum-sensing"). In mature biofilms, they are connected by fluid channels, that transport metabolites. In contrast to bacteria present in planktonic form, they are more resilient against physical and biological damage e.g. growth-dependant antimicrobials or the host immune system [37].

Table 3 - Variables important in cell attachment and biofilm formation. Source: [36]

Properties of the substratum	Properties of the bulk fluid	Properties of the cell
• Texture or roughness	• Flow velocity	• Cell surface hydrophobicity
• Hydrophobicity	• pH	• Fimbriae
• Condition film	• Temperature	• Flagella
	• Cations	• Extracellular polymeric substances
	• Presence of antimicrobial agents	

Formation of biofilm requires certain conditions of the surface, the microbes and the surrounding fluid, corresponding to the host in a medical environment, as shown in Table

3. It was found, that the extent of microbial colonization increases by the surface roughness [38], caused by lower shear forces and an increased surface area [36].

It also has been found, that the degree of hydrophobicity plays a role, since bacteria attach faster to hydrophobic surfaces than to hydrophilic. Being in contact with a polymer containing fluid, a surface will be coated by a layer of these polymers, referred to as conditioning film. In case of indwelling devices, the environmental fluids are blood, urine, bile and salivary respiratory fluids consisting of proteinaceous and polysaccharide components which are rapidly coating implanted biomaterials by a conditioning film [39]. The surrounding fluid influences the development furthermore by its physical and chemical composition. Important parameters are temperature, pH-level, nutrient levels and ionic strength.

From the side of the microbes, the properties of the microbial cells regarding hydrophobicity, surface structures like fimbriae, flagella and other proteins and the presence of extracellular polymeric substances are affecting the extent of adhesion to surfaces. The initial attachment of bacteria is more likely on rough, hydrophobic surfaces already coated by a conditioning film [36]. Which constellation effects an acceleration of the initial adherence, depends also on the certain bacteria.

In case of *Staphylococcus epidermidis* this initial adherence is based on nonspecific conditions like surface tension, hydrophobicity or electrostatic forces [25]. This phase is ensued by an accumulative phase, during which cells of *Staphylococcus epidermidis* begin to connect to each other mediated by polysaccharide intercellular adhesion [40] and the development of a biofilm begins. In the case of *Staphylococcus aureus,* the initial phase is more conditional to specific factors, such as ligands originating from the host tissue like fibronectin, fibrinogen and collagen. Furthermore, the presence of a foreign body is a conducive factor [41]. The development of a periprosthetic joint infection is a complex interaction of different factors [42], as shown in Figure 4.

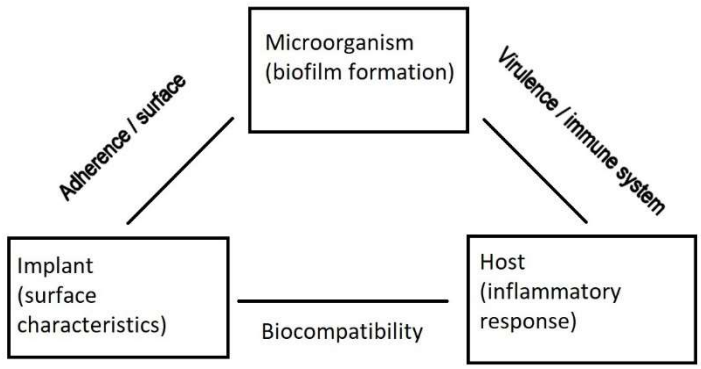


Figure 4 - Interaction between the microorganism, the implant and the host in the pathogenesis of implant-associated infections. Adapted from: [42]

In vitro studies showed, that the tolerance against antibiotics increases within days with the development of biofilms [43]. A retrospective study on elderly patients with periprosthetic joint infections treated with a combination of rifampicin and levofloxacin and debridement retaining the endoprosthesis, found a significant correlation between the time between onset of the symptoms, begin of the therapy and the treatment failure rate. Analysis showed failure rates ranging from 16.6%, when treatment started at least within four weeks after infection onset over 34.8% (begin of treatment two to six month) up to 69.2%, when therapy began after six month or more after onset of symptoms [44]. In a prospective controlled study analysing the effectiveness of biofilm-active antibiotic treatment in case of early postoperative (less than one month postoperative) and acute hematogenous infections, superior outcomes of the biofilm-active antibiotics have been observed [45]. The period of time, after which a mature biofilm is present, varies between 14 and 90 days [46].

Routes of periprosthetic joint infection

There are different transmission routes for periprosthetic joint infections: peri- or direct postoperative contamination of the wound, hematogenous infection by bacteraemia, per continuitatem by a contiguous focus of inflammation or by inoculation after penetrating trauma.

The risk of a hematogenous periprosthetic joint infection was found to be small at 0.3% over 6 years. It seems, that septicaemia or chronic bacteraemia originating e.g. from chronic soft tissue infects is more dangerous than transient bacteraemia [47]. In patients with a proven *Staphylococcus aureus* bacteraemia, a risk of 34% of infection of an implanted total arthroplasty was observed [48]. The percentage of hematogenous infection in a retrospective cohort study of 35 patients with 40 episodes of infected knee arthroplasty were determined at 38% [49]. Acute and chronic postoperative infections are

presumed to be caused by intraoperative inoculation of bacteria, either with an acute clinical course within 3-4 weeks after surgery or with an insidious course over a period of months to years. Despite the pathogenesis in both clinical entities is the same (i.e. perioperative colonization of the prosthesis), the clinical manifestation depends on the virulence of the infecting pathogen.

Classification of periprosthetic joint infections

In case of an infected total arthroplasty, it is of crucial importance to identify the present pathogenesis correctly, since the retainment or removal of the prosthesis with corresponding implications for the patient depends on this. Several classifications have been proposed, but to date no classification has been accepted as “gold-standard”. The classification of periprosthetic joint infections is possible according to the route of infection as mentioned above and to the onset of symptoms after implantation. Some classifications use additional characteristics, like the medical and immune status of the patient, the local condition of the extremity [50], positive microbial findings [51] or anatomical extent of infection [52]. Depending on the length of the period, which has passed between the index operation and occurrence of a periprosthetic joint infection, a subdivision into different groups is possible, as shown in Table 4. The duration of the respective periods has changed in the last decades and differs between the corresponding classifications. It has been proposed to classify infections that occur within four weeks after surgery as early infections and infections occurring from fifth postoperative week on as late or chronic infections [50]. Other authors propose a subdivision before and after the twelfth postoperative week [33,53] or before and after end of the sixth postoperative month [54].

Table 4 - Classification of periprosthetic joint infections. Adapted from:[55]

	Acute	**Chronic**
Perioperative	Early postoperative (<4 weeks after surgery)	Delayed ("low grade") infection (>4 weeks after surgery)
Hematogenous	<3 weeks after onset of symptoms	>3 weeks after onset of symptoms
Biofilm	Immature	Mature
Clinical findings	Acute pain, fever, redness, effusion, persistent wound secretion	Chronic pain, sinus tract, early loosening of implants
Typical microorganisms	Highly-virulent: *Staphylococcus aureus*, streptococci, enterococci, gram-negative bacteria (e.g. *E. coli*; *Enterobacter*, *Pseudomonas aeruginosa*)	Low-virulent: coagulase-negative staphylococci (e.g. *Staphylococcus epidermidis*), anaerobes (e.g. *Propionibacterium acnes*)
Treatment	Debridement and change of mobile parts, retainment of prosthesis possible	Exchange of prosthesis (one-, two- or three staged)

Microbial spectrum

The most frequent bacteria commonly associated with periprosthetic joint infections are coagulase-negative staphylococci (30-43%), *Staphylococcus aureus* (12-23%) and polymicrobial infections (10-20%), as shown in Table 5.

Table 5 - Frequency of microorganisms causing periprosthetic joint infection. Source: [56]

Microorganism	Frequency (%)
Coagulase-negative staphylococci	30-43 %
Staphylococcus aureus	12-23 %
Streptococci	9-10 %
Enterococci	3-7 %
Gram-negative bacilli	10-17 %
Anaerobes	2-4 %
***Candida* spp.**	1-3 %
Polymicrobial	10-20 %
Unknown (culture false-negative)	10-30 %

In 10-30% of cases, no pathogen is detectable in spite of clinical apparent infection [56]. Bacteria, against which primarily biofilm-active antibiotics are not available, like rifampicin-resistant staphylococci or quinolone-resistant gram-negative rods, are referred to as “difficult-to-treat” pathogens [57]. Varying percentages of methicillin-resistant bacteria have been reported. For example, in a cohort of 37 infected hip arthroplasties 5 out of 35 patients were found to be infected by MRSA [58]. On the other hand, 2014 Achermann et al. found that most (24 of 26) coagulase-negative staphylococci were methicillin-resistant [59].

Definition of periprosthetic joint infection

Several proposals for the definition of the presence of a periprosthetic joint infection have been made, but to date there is no commonly accepted gold-standard [60]. Despite certain differences, definitions are commonly based on the results of joint aspiration or deep tissue culture and histopathologic analysis of this samples, respectively. Other blood tests, like C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), the macroscopic local finding within revision, existence of a sinus tract and the result of histologic analysis (frozen section) of tissue obtained during surgery [61].

The American Musculoskeletal Infection Society (MSIS) proposed 2011 a combination of criteria for the definitive presence of a periprosthetic joint infection while emphasizing, that an infection can still be present when less criteria are met [62].

Alongside, the Infectious Disease Society of America proposed 2013 recommendations for diagnosis and treatment of periprosthetic joint infections [64]. In contrast, some authors state, that in these guidelines the conventional way of diagnostic procedures for periprosthetic joint infection is depicted not taking recently found methods of diagnosis like sonication into account [57]. One of the recently conducted definitions is shown in Table 6.

Table 6 - Definition for the presence of a periprosthetic joint infection. Adapted from: [63]

Definition of a periprosthetic joint infection: presence of a periprosthetic joint infection in case of ≥ 1 criteria present	
	Criteria
Clinical findings	sinus tract, intraarticular pus
Histopathology	acute inflammation in periprosthetic tissue
Cell count	>2.000/µl leukocytes >70% neutrophils
Microbial findings	Detection of pathogen in:
	≥ 2 biopsies (≥1 in case of high-virulent pathogens)
	synovial fluid
	Sonication ≥50 colonies/ml

Diagnostic means to prove periprosthetic joint infections

Follow-up radiography is useful to find loosening of endoprosthetic components or signs of infection e.g. osteolysis, periosteal reaction [65] or inadequate osteopenia. Smears obtained from eventually present sinus tracts are considered as not useful, as the skin-flora could distort the result and therefore delay appropriate therapy [46]. In Table 7 the commonly used pre- and intraoperative routine-tests are listed.

Table 7 - Routinely pre- and intraoperative used tests for diagnosis of periprosthetic joint infection. Adapted from: [66]

Category	**Description of the diagnostic tests**
Preoperative	
• **Clinical history and examination**	Persistent joint pain; fever; chills or rigors without known aetiology, warmth or effusion of the joint, sinus tract
• **Haematological tests**	Leukocyte count and differential, erythrocyte sedimentation rate; C-reactive protein level
• **Synovial fluid aspiration**	Leukocyte count and differential, Gram stain and culture
• **Biopsy**	Histopathology, Gram-stain and culture
• **Radiographic imaging**	Scintigraphy by technetium ($Tc^{99}m$), gallium citrate (Ga^{67}) or indium (In^{111}) scan, accuracy improved by combination with labelled leukocyte or monoclonal antigranulocyte antibody scan
• **Positron emission tomography**	Fluorine-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography
Intraoperative	
• **Periprosthetic tissue**	Histopathology; Gram-stain and culture
• **Explanted prosthesis**	Culture (sonication)

Diagnosis of periprosthetic joint infections can be difficult in cases with little or absent clinical symptoms pointing to a septic origin. To distinguish present symptoms from an aseptic loosening is from clinical experience in some cases not adequately possible.

Table 8 - Sensitivity and specificity of commonly used diagnostic tools in diagnosis of periprosthetic joint infection. Source: Adapted from [21], modified after [63]

Definition criteria	Sensitivity	Specificity
Cutaneous sinus tract communicating with prosthesis	20-30%	~100%
Acute inflammation in periprosthetic tissue histopathology	95-98%	98-99%
Synovial fluid leukocyte count and differential		
• (> 2.0 x 10^9/l leukocytes, >70% neutrophils)	95%	98%
Visible purulence (wound secretion, pus around the prosthesis)	20-30%	100%
Microbial growth		
Synovial fluid	60-80%	97%
• Periprosthetic tissue	70-85%	92%
• Sonication fluid (> 50 CFU/ml)	85-95%	95%

In other medical disciplines, the tissue- or fluid culture is sometimes referred to as gold-standard, but bearing in mind chronic low-grade infects with bacteria present in their stationary sessile form not always detectable by cultural methods, this is not applicable in diagnosis of periprosthetic joint infections. An overview about the sensitivity and specificity of commonly used diagnostic tools adapted from Zimmerli et al. 2004 [21], where the leukocyte count is modified according to Renz et al. 2016 [63], is shown in Table 8.

Microbial and cytological analysis of aspirated joint fluid

Values concerning the accuracy of the results of previous cultural methods are varying, as some authors state in 5-37% of cases a false positive and in 2%-18% of cases a false negative result [61] of fluid as well as tissue cultures. In routinely performed aspirations before revision surgery of total hip arthroplasty without clinical findings indicating an infection, a sensitivity of 60% and a positive predictive value of 15% has been found [67], while the same authors found regarding routinely performed aspiration before revision of knee arthroplasty a sensitivity of 55% and a positive predictive value of 85% [68].

Another study compared culture of aspirated joint fluid to culture of intraoperative obtained tissue samples and found a sensitivity of 82%, a specificity of 91% with resulting positive and negative predictive values of 74% and 94%, and an accuracy of 89%, respectively [69]. Additionally, it has been shown, that both, the leucocyte count and neutrophil percentage of the joint aspirate, can be useful diagnostic parameters for diagnosis of non-acute infections [70].

The threshold of leukocyte count and neutrophil percentage, which diagnoses periprosthetic joint infection differs from author to author. Trampuz et al. found 2004 regarding knee endoprostheses a sensitivity of 94% and a specificity of 88% for a threshold of 1,700 leukocytes/µl and a sensitivity of 97% and a specificity of 98% for diagnosis of periprosthetic joint infection in case of a cut-off set at neutrophil percentage above 65% [71]. Others proposed a synovial fluid leukocyte count threshold of 2.500/ml (corresponding to 2.5 leukocytes/µl) [70], respectively, 50/ml (corresponding to 50,000/µl) [72] and regarding neutrophil percentage a cut-off above 60% [70], respectively, 50% [72]. Recently conducted definition criteria recommend 2.000/ml leukocytes and 70% of neutrophils as threshold for both hip and knee arthroplasties [63].

Microbiological analysis of intraoperative tissue samples

The diagnostic use of culture of intraoperative collected tissue samples was found to be superior compared to the use of joint aspirates regarding sensitivity (82% vs. 64%) and specificity (98% vs. 96%) [73]. To achieve this value at least three, if possible five to six tissue samples should be collected [74]. Furthermore, it is recommended to take the samples from periprosthetic tissue [46].

Still, the increased sensitivity is not satisfactory and the risk to find bacteria due to contamination is not negligible. In a series of 138 revision total hip arthroplasties, 42 positive cultures of tissue samples were obtained, standing in contrast to only one of these patient showing signs of infection later on within a follow-up period of 48 month [75]. On the other hand, Atkins et al. found only 65% of positive tissue cultures in prospective study with 297 patients treated with hip revision arthroplasty of which 41 were defined as infected, which is why it was recommended to take multiple samples [74]. On the basis of several studies showing false-positive or false-negative results of microbial analysis of intraoperative tissue samples, Bauer et al. concluded 2006, that intraoperative cultures are a “tarnished gold standard” for the diagnosis of periprosthetic joint infections [60].

In case of highly-virulent pathogens like *Staphylococcus aureus* a single positive sample is sufficient for diagnosis of a periprosthetic joint infection. In cases of pathogens with a lower virulence, at least two positive samples showing the same pathogen are required for diagnosis [76].

Histopathologic analysis of intraoperative tissue samples

Histological examination was found to be more sensitive compared to conventional cultural methods [73]. Of particular interest is the tissue enclosing the prosthesis, referred to as periprosthetic membrane. It is a layer of connective tissue surrounding the implant being present also in firmly fixed prostheses with a thickness ranging from 0.1 to 0.3 mm around the femoral component to more than 1.0 mm around the acetabular component of a hip prosthesis [77,78]. In non-cemented endoprostheses it is located between bone and implant, in cemented endoprostheses between bone-cement and bone. Associated with this biofilm osteolyses of various extent can be observed, which are caused by micromovement of the prosthesis and by osteolytic activity of cells situated in the periprosthetic membrane [79].

The histological examination of this membrane is of great interest due to the possibility of an early diagnosis in contrast to cultural methods. According to its histological characteristics it can be classified after the consensus classification defined by Morawietz and Krenn. They defined four types of periprosthetic membranes: “wear particle induced type” or type I; “infectious type” or type II; “combined type” (aspects of type I and type II occur simultaneously; type III) and “indeterminate type” or type IV. They examined the periprosthetic membranes of 370 patients and noted a high correlation of 89.7% between histopathological and microbiological diagnosis and an inter- observer reproducibility of 85% using the proposes classification [80]. Following research found similar values with sensitivity of 87 % and a specificity of 100 % [81]. Gram stain of periprosthetic tissue is known to have a high specificity of up to 95%, but its sensitivity is poor below 25% [56], which is why it is not recommended on routine examination anymore.

Sonication

Cultures of joint aspirate and tissue samples are especially in low-grade infections and cases of prior antibiotic therapy frequently false-negative [82]. One possible explanation is, that these methods cannot securely cover the biofilm adhering to implanted endoprostheses. To strip the biofilm off the implants, besides sonication several other methods have been proposed e.g. scraping or swabbing off the biofilm, use of enzymes, anticoagulants or other detergents and vortexing, what describes the mixing of the implants within a solution [83].

Recent studies found, that an effective sampling of biofilms can be achieved by sonication. A prospective trial, comparing culture of tissue samples with culture of samples obtained by sonication, found a sensitivity of 60.8% compared to 78.5%, respectively. Specificity values were similar at 99.2% for tissue sample cultures and 98.8% for sonicate sample cultures. In patients with prior antibiotic therapy, the difference was observed to be increased with a specificity of tissue samples of 45% compared to sonication samples with 75% [84]. Compared to histological examination, a prospective study on 59 patients found regarding sonicate fluid cultures a sensitivity of 91% [81], thereby being more sensitive than the analysis of periprosthetic membranes according to Morawietz and Krenn [80] with a sensitivity found to be 87%. Additionally, it has been shown, that further improvement of validity of diagnosis can be achieved by combining both methods [81].

Three-phase bone scintigraphy

Being of little help to differentiate between aseptic or septic loosening, 3-phase-bone scintigraphy can be a useful tool to out-rule aseptic or septic loosening in cases with unclear or negative findings in plain radiography given a certain interval after the last revision surgery. As mentioned above, this makes sense eight to twelve month after last revision depicting until then the physiological postoperative remodelling processes of the bone. It was found to have in combination with plain radiography a satisfactory negative predictive value of 88% accompanied by a poor positive predictive value of 30% [85].

FDG-PET/CT

18F-fluorodeoxyglucose is a chemical compound that is transported into cells by a glucose transporter and is metabolized to fluorodeoxyglucose-6-phosphate (FDP). The latter one accumulates in activated lymphocytes, neutrophils, and macrophages with minimal decrease over time since it cannot be further metabolized [86]. Being a non-specific marker by this mechanism, FDG accumulates in infected tissue but also in tissue presenting aseptic inflammation and malignant lesion [87].

In a study on 50 symptomatic patients, FDG-PET was found to be useful for differentiation between septic and aseptic hip arthroplasty failure with 91% sensitivity, 92% specificity, resulting in 91% accuracy in 50 patients [88]. Another study on 53 patients with hip prostheses and 36 patients with knee prostheses, with each group including 12 confirmed

infections, a correct diagnosis in 11 out of 12 cases in the respective group was found, entailing a sensitivity of 91.7% and 92%, respectively. In 41 noninfected cases, FDG-PET was correct in all cases except one [89].

Treatment of periprosthetic joint infections

The therapy of periprosthetic joint infections in Germany is not uniformly regulated [90]. Research over the last decades initiated new treatment proposals with a possible retention of infected endoprostheses under certain circumstances standing in contrast to past therapeutic procedures. The strategy must be adjusted alongside the given anamnestic, clinical, laboratory-chemical and microbiological findings.

General principles

As already stated, bacteria in chronic periprosthetic joint infections are present in a biofilm adhering to the surface, being more resilient against local or systemic antibiotics, thus former approaches implied removal of the endoprosthesis [51].

Systemic antibiotic therapy

In periprosthetic joint infections, the results of in-vitro testing differ from the efficacy of the treatment in-vivo [45]. This effect is caused by bacteria being present in their stationary form within a biofilm on the implant-surface not growing logarithmical, while the antibiogram is obtained from the more vulnerable planktonic form of the bacteria [91]. Hence, only bio-film active bactericidal antibiotics are able to attack pathogens of periprosthetic joint infections effectively. In a large multicentre-study, it was found that biofilm-active antibiotics given within the first 30 days influenced the outcome pointing to the importance of a correct evaluation of the biofilm [92]. In tests, the efficacy of rifampicin against staphylococci as a biofilm-active agent has been observed [93]. Quinolones have been shown to be effective against the biofilm of gram-negative rods [94] while not being able to impede staphylococci.

On the other hand, the described lower division rate also entails, that antibiotics taking effect on the synthesis of the cell wall are not effective against biofilm-developing pathogens in chronic implant associated infections [91]. This includes all beta-lactams (penicillin derivatives, cephalosporines, carbapenems) and glycopeptides (vancomycin,

teicoplanin) [95]. An example of a current pathogen-specific recommendation for antibiotic therapy is listed in Table 9. Administration of antibiotics is recommended initially intravenous for two to four weeks. This recommendation is caused by the usually increased bacterial count at begin of therapy. To diminish the risk of development of resistances, the initial concentration of antibiotics should be as high as possible. An interval of two-week intravenous administration seems to be sufficient [96]. Additionally antibiotics, against which a development of resistance is known, should be avoided in the initial phase until a sufficient reduction of bacterial count by debridement and intravenous antibiotics is achieved [97].

As already mentioned, rifampicin has been shown to be effective against staphylococci especially in biofilms [98]. It has a bioavailability of 70-90% [99]. To prevent the development of a resistance against rifampicin by non-selected staphylococci entering through the wound, rifampicin should be withheld until the wound is dry and the Redon drains are removed, as the risk of resistances against rifampicin otherwise seems to be increased [100]. For further minimization of risk of resistance-development, rifampicin should be administered in combination with a second drug, e.g. quinolones, tetracyclines or cotrimoxazole [25], as emergence of a resistance of staphylococci is the consequence of a single point mutation, which is found more frequently under mono-therapy than under combination-therapy [101]. In infections by methicillin-resistant staphylococci the combination with vancomycin is recommended.

Table 9 - Recommended antibiotic therapy in case of periprosthetic joint infection. Adapted from: [21]

Pathogen	**Antibiotic**	**Dose**	
***Staphylococcus* spp.**			
- Oxacillin-/Methicillin-susceptible	Flucloxacillin	4 × 2 g	IV
	(or Fosfomycin)	(3 × 5 g)	IV
	+		
	Rifampicin	2 × 450 mg	p.o.
	for 2 weeks, followed by (depending on antibiogram)		
	- Levofloxacin or	2 × 500 mg	p.o.
	- Cotrimoxazole or	3 × 960 mg	p.o.
	- Doxycycline or	2 × 100 mg	p.o.
	- Fusidic-acid	3 × 500 mg	p.o.
	+		
	Rifampicin	2 × 450 mg	p.o.

- Oxacillin-/Methicillin-resistant	Daptomycin or Vancomycin or Fosfomycin) + Rifampicin for 2 weeks, followed by same regimens as for Oxacillin-/Methicillin-resistant Staphylococci	1 × 8 mg/kg 2 × 1 g (3 × 5 g) 2 × 450 mg	IV IV IV p.o.
- Rifampicin-resistant	Vancomycin or Daptomycin for 2 weeks, followed by: long-term suppression ≥ 1 year, depending from susceptibility (e.g. cotrimoxazole, Doxycycline or Clindamycin)		
***Streptococcus* spp.**	Penicillin G or Ceftriaxone for 2 weeks, followed by Levofloxacin or Amoxicillin	4 × 5 Mio. U 1 × 2 g 2 × 500 mg 3 × 1000 mg	IV IV p.o. p.o.
- *Enterococcus* Spp. Penicillin-susceptible	Ampicillin + Gentamicin (+/- Fosfomycin) for 2-3 weeks, followed by Amoxicillin	4 × 2 g 2 × 60–80 mg (3 × 5 g) 3 × 1000 mg	IV IV (IV) p.o.
- Penicillin-resistant	Vancomycin or Daptomycin + Gentamicin (+/- Fosfomycin) for 2 - 4 weeks, followed by Linezolid (max. 4 weeks)	2 × 1 g 1 × 10 mg/kg 2 × 60–80 mg 3 × 5 g 2 × 600 mg	IV IV IV IV p.o.
- Vancomycin-resistant (VRE)	Daptomycin or Linezolid followed by individual regimens, removal of endoprosthesis or life-long suppression necessary	1 × 10 mg/kg 2 × 600 mg	IV p.o.
Gram-negative bacteria			
- Enterobacteriaceae (*E. coli, Klebsiella, Enterobacter* etc.)	Ciprofloxacin	2 × 750 mg	p.o.
- Nonfermenters (*Pseudomonas aeruginosa, Acinetobacter*)	Piperacillin/Tazobactam or Meropenem or Ceftazidime + Tobramycin for 2–3 weeks, followed by Ciprofloxacin	3 × 4.5 g 3 × 1 g 3 × 2 g 1 × 300 mg 2 × 750 mg	IV IV IV IV p.o.
- Ciprofloxacin-resistant	depending on susceptibility of pathogen: Meropenem 3 × 1 g i.v., Colistin 3 × 3 Mio. E i.v., Fosfomycin 3 × 5 g i.v., followed by oral suppression (individual) or removal of endoprosthesis		

Anaerobes			
- Gram-positive (*Cutibacterium* (formerly known as *Propionibacterium*), *Peptostreptococcus, Finegoldia magna*)	Penicillin G or Ceftriaxone + Rifampicin for 2 weeks followed by Levofloxacin or Amoxicillin + Rifampicin	4 × 5 Mio. E 1 × 2 g 2 × 450 mg 2 × 500 mg 3 × 1000 mg 2 × 450 mg	IV IV p.o. p.o. p.o. p.o.
- Gram-negative (Bacteroides)	Ampicillin/Sulbactam for 2 weeks, followed by Metronidazole	3 × 3 g 3 × 400 mg	IV p.o.
***Candida* spp.**			
- Fluconazole-susceptible	Caspofungin or Anidulafungin for 2 weeks, followed by Fluconazole (suppression ≥ 1 year)	1 × 50 mg (on 1. day 70 mg) 1 × 100 mg (on 1. day 200 mg) 1 × 400 mg	IV IV p.o.
- Fluconazole-resistant	individual (e.g. Voriconazole 2 × 200 mg p.o.), removal of endoprosthesis or life-long suppression necessary		
culture-negative	Ampicillin/Sulbactam for 2 weeks, followed by Levofloxacin or cotrimoxazole + Rifampicin	3 × 3 g 2 × 500 mg 3 × 960 mg 2 × 450 mg	IV p.o. p.o. p.o.

In case of a staged therapy, biofilm-active antibiotics should not be used until reimplantation, since there is, apart from antibiotic loaded spacers, no indwelling device with an adhering biofilm present after the initial explantation – in this constellation intravenous beta-lactam antibiotics are to be preferred [95].

Quinolones can impede staphylococci in-vitro efficiently, but are not able to penetrate it if present in biofilms. In the class of quinolones, therapy of periprosthetic joint infection by gram-negative bacteria with ciprofloxacin has been well documented [94], followed by moxifloxacin and levofloxacin. Reliable results of studies with sufficient number are to be conducted yet, but following the available studies, they seem to show a good efficacy in combination with rifampicin [99].

Against the background of increasing frequency of resistances, an alternative combination of rifampicin is possible with fusidic acid. Studies on fusidic acid in combination with rifampicin found adequate results [102,103]. Another possible combination is linezolid. In an animal-model study, it was found to be equally efficient as the combination of vancomycin with rifampicin [104].

The optimal duration of administration of antibiotics has not been analysed by a controlled comparing study yet. Recommendations depend on the type of therapy. Regarding infections of hip-arthroplasties treated by a one-stage revision or a two-stage revision with short interval, respectively, a three-month antibiotic administration is commonly found in the literature. Regarding treatment of infections of knee arthroplasties, a six-month administration can be found [45,64], although recent studies have been able to show, that a three-month administration can be also sufficient [105].

Local antibiotic therapy

The main advantage of local antibiotic therapy is, that high local concentrations of antibiotics can be achieved, while systemic side effects can be reduced. The drug delivery systems needed for an local application of antibiotics can be subdivided into non-bio-degradable and bio-degradable carriers [106]. Non-biodegradable carriers, like bone-cement spacers or beads, have been well established in the therapy of osteomyelitis [107]. Concerning bio-degradable carriers, a wide range of products have been conducted [108].

Antibiotic-loaded bone cement

To increase local concentration of antibiotics and minimize dead space after explantation of implants, PMMA-Spacer or beads loaded with antibiotic can be used to serve as local drug delivery system. Additionally, they are also used to prevent shortening of the joint and surrounding soft tissue, which is especially important in knee explantations. Antibiotic-loaded PMMA-spacers are available off-the shelf but can also be made by the surgeon by forming it to the clinical needs after adding antibiotics, if necessary reinforced by a metal rod. They can be subdivided in monobloc-spacer and articulating spacers, however, data which option is to be preferred is conflicting. As already mentioned above, the rate of infection control seems to be superior when using antibiotic-loaded bone cement [16].

Antibiotic release decreases over time, hence a main drawback of PMMA-Spacer and beads is the necessity to explant them as they become a foreign body, which can serve bacteria as a surface to adhere to. Regarding beads, common recommendation is to

exchange them after 10-14 days. Masri et al. demonstrated 1998 sufficient therapeutic doses eluting from high-dose bone cement spacers in two-stage revisions up to four month after implantation in a prospective study including 49 patients [109]. In contrast, in vitro studies found only little long-term elution of antibiotics from antibiotic-loaded spacer [110]. The addition of antibiotics can endanger the mechanical integrity of bone cement, therefore an amount not exceeding 10% of the whole PMMA-amount is recommended [111].

Table 10 - Overview of antibiotics added to bone cement spacer. Adapted from [112]

Microorganism (S = susceptible, R = resistant)	**Antimicrobial**	**Dose (g per 40 g cement)**	**Mechanical stability**	**Synergistic elution**	**Commercial product available**
***Staphylococcus* spp.**	Gentamicin +	1 g			
- Oxacillin-/methicillin-S	Clindamycin	1 g	++	+	Yes
- Oxacillin-/methicillin-R	Gentamicin +	0.5 g			
	- Daptomycin or	2 g	+	+	No
	- Vancomycin	2 g	++	+	Yes
***Streptococcus* spp.**	Gentamicin +	0.5-1 g			
	- Clindamycin or	1 g	++	+	Yes
	- Cefuroxime	1-3 g	+	No data	No
***Enterococcus* spp.**	Gentamicin +	0.5 g			
- Vancomycin-S/ aminoglycoside-S or R	Vancomycin	2 g	++	+	Yes
- Vancomycin-R/	Gentamicin +	0.5 g			
aminoglycoside-S or R	- Linezolid or	1 g	+	+	No
	- Daptomycin or	2 g	+	+	No
	- Fosfomycin	1-2 g	+	No data	No
Enterobacteriaceae	Gentamicin	1 g			
- Aminoglycoside-S	(+/- Clindamycin)	1 g	++	+	Yes
- ESBL-producer or	Gentamicin +	0.5 g			
aminoglycoside-R	Meropenem	2 g	No data	No data	No
- Carbapenem-R or	Gentamicin +	0.5 g			Only: Colistin +
aminoglycoside-R	Colistin	1-2 g	+	+	Erythromycin
Nonfermenters	Gentamicin +	0.5 g			
- Aminoglycoside-S and Fluoroquinolone-S	Ciprofloxacin	2 g	+	+	No
- Multi-R	Gentamicin +	0.5 g			Only: Colistin +
	- Colistin or	1-2 g	+	+	Erythromycin
	- Fosfomycin	1-2 g	+	+	No
Anaerobes (gram positive)	Gentamicin +	1 g			
	Clindamycin	1 g	++	+	Yes
***Candida* spp.**	Gentamicin +	0.5 g			
	- Amphotericin B liposomal (Ambisome) or	0.2-0.3 g	+	No data	No
	- Amphotericin B non-liposomal (Fungizone) or	0.2-0.8 g	+	No data	No
	- Voriconazole	0.3-0.6 g	No data	No data	No

Due to their mechanical and microbial characteristics, commonly added antibiotics are vancomycin, gentamicin and tobramycin. A synergistic elution effect has been reported for combination of vancomycin and gentamicin [109]. Kühn et al. proposed 2017 combinations of local antibiotics and analysed the respective mechanical stability and synergistic elution [112], which are summarized in Table 10.

Possible complications of implanted spacers are dislocation or fracture of the spacer and fracture of the adjacent bone. In a retrospective study on 82 cases of infected hips in which a handmade articulating single sized spacer was used, as complications regarding the spacer have been found: spacer dislocation in 17%, spacer fracture in 9% and femoral fractures in 13.6% of cases [113].

Antibiotic-loaded bone grafts and bone graft substitutes

Another option to achieve a therapeutic local concentration of antibiotics are antibiotic-loaded bone grafts or substitutes, respectively. In an animal-model study, no differences in histopathological and radiological findings between conventional and tobramycin-loaded bone grafts have been identified within 12 weeks after implantation [114].

Targets of the use of bone graft substitutes loaded with antibiotics are waiving of the otherwise necessary removal, waiving of a second exposure for the origination site, dead space management alongside with preferably guidance for tissue for defect repair and a phase of secondary drug release during degradation, extending the maximum period of local therapeutic antibiotic doses being present. Commonly used bone graft substitutes are collagen sponge, lactic acid polymers and calcium phosphate based ceramics [108].

Therapy regimen

The traditional therapeutic approach in cases of periprosthetic joint infection is a two-stage exchange consisting of the initial explantation alongside with a thorough debridement of infected tissue followed by a certain period of administration of antibiotics (usually at least 6 weeks). The reimplantation is performed 14 days after the last antibiotic intake. Reimplantation is performed, if clinical signs are auspicious. Confirmation of eradication of infection is either achieved by a negative tissue biopsy or by negative intraoperative tissue samples collected during reimplantation surgery [25].

By the research of the last decades, biofilm-active antibiotics were found to be able to treat biofilm-developing bacteria in the initial phase [45]. To date, the correct estimation of the maturity of the biofilm is of crucial importance, as it entails the decision to retain or remove the implants. In early postoperative or acute hematogenous infections with an

onset of symptoms less than a few weeks ago the biofilm is not fully developed. An exact length for this period have not been stated yet, commonly used periods are ranging between one to four weeks [45,49,115,116]. Given good soft-tissue conditions, an immature biofilm and a known pathogen, against which biofilm-active antibiotics are available, a retention of the prosthesis along with thorough debridement and exchange of mobile parts is recommended [117].

In case of a chronic infection with a mature biofilm, an exchange of the prosthesis is necessary. In absence of complicating factors, a one-stage revision with exchange of all implants, thorough debridement and use of antibiotic-loaded cement is recommended [118]. Otherwise, a two-stage revision with an implant free interval, with or without spacer, is recommended.

Usually, a short-interval of two to three weeks seems to be sufficient. In cases of “difficult-to-treat” pathogens or compromitted soft-tissue, the interval is recommended to be six to eight weeks [55]. In chronic recurring infects, a three-stage strategy can be chosen, with an additional spacer exchange and debridement two to three weeks after initial explantation of the endoprosthesis [119].

In cases of severe recurrent infection, an arthrodesis should be considered, either by implants or by bone grafts combined with a temporal external stabilisation. Amputation of the limb is the ultima ratio. In cases of unwanted or strictly contraindicated surgical therapy, a long-term antibiotic therapy is possible instead [64,120].

2 Material and methods

2.1 Study design

The conducted study consists of a pro- and retrospective cohort study at the “Vivantes Klinikum im Friedrichshain” in Berlin, Germany, a tertiary healthcare centre. Patients were identified by the means of ICD-classification stored in the electronic medical charts. The used ICD-diagnosis for primary identification was T84.5 (Infection and inflammatory reaction due to internal joint prosthesis). If a periprosthetic joint infection in accordance with the criteria noted below was present, data was collected from the patient charts and recorded in a case report form. Patient charts were available in written or in electronical form. Data regarding outcome was acquired by a survey consisting of general questions and the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) filled out by the patients themselves. The WOMAC-Index was chosen, because it is applicable for hip- and knee-associated pathologies equally [121].

2.2 Study population

All patients, who fulfilled the inclusion criteria as listed below, with an ICD diagnosis classified as T84.5 of the hip or the knee and who have been admitted to the orthopaedic department of “Klinikum im Friedrichshain” in the years from 2010 to 2015, were primarily included. For assessment and usage of the data collected within the outcome-analysis a valid declaration of consent was required.

2.3 Performed regimen of diagnostics and therapy

Common basic diagnostic like medical history, clinical examination and radiography was performed on every admitted patient. In septic patients, blood cultures were taken. As infectious parameter, the leukocyte count and the CRP value were determined. In case of suspicion of an acute postoperative or hematogenous infection by clinical findings, usually an aspiration of the affected joint was performed. In case of suspicion of a chronic infection, either an aspiration or an arthroscopic biopsy of the synovial tissue were usually performed. At least two weeks pause to any prior antibiotics taken were respected.

Aspirations were performed in the operation theatre under sterile conditions after

disinfection of the skin using a 14G or 21G needle, respectively. The punctate was filled in a smear tube and in a pair of blood culture bottles, if enough fluid was obtained.

Biopsies were performed as arthroscopic biopsies under sterile conditions and general anaesthetic. Samples were collected by an arthroscopic biopsy forceps before usage of arthroscopic fluid. Usually three to four tissue samples were collected: two to three smear tubes, a pair of blood culture bottles and one tube for the histopathologic examination were filled. Specimen were incubated for 14 days.

In case of acute postoperative or hematogenous infections, dependent on the local intraoperative findings, the adjacent soft tissue status and the general medical status of the patient, the respective therapy was chosen. Alongside irrigation and debridement either an exchange of mobile parts, a one-stage exchange of all components or a long term two-stage exchange were performed. In chronic infections, a long term two-stage exchange was deemed necessary.

In two-stage exchange of infected knees either articulating or monobloc high-dose antibiotic-loaded spacer were used. In two-stage exchange of infected hips partially no spacer and partially high-dose antibiotic-loaded spacer were used. Spacers used were self-made. They were either made from pre-loaded Copal® (Heraeus Medical, Hanau, Germany) or from Palacos® (Heraeus Medical) bone-cement loaded with antibiotics according to the antibiogram. Antibiotics used were vancomycin, gentamicin and clindamycin.

Administration of antibiotics was withheld until collection of tissue samples from the periprosthetic tissue during the first surgery performed out of septic reasons. Dual antibiotics were administered intravenously for one to two weeks postoperatively and afterwards orally until end of the sixth to eighth week. Antibiotics were adapted according to the results of the microbial examinations, if necessary. In two-stage exchanges with unsuspicious course of therapy, an arthroscopic biopsy of the affected joint was performed two weeks after the last intake of antibiotics. If the microbial and histopathologic results of this biopsy were negative, a reimplantation was performed. Bone cement used in reimplantation was concordant to the bone cement used for spacers high-dose antibiotic-loaded cement.

If there were signs of persistence or positive microbial or histopathological findings in the biopsy prior to reimplantation, a revision with irrigation, debridement and exchange of the spacer, if used, was performed and subsequently the same regimen as after the initial explantation was carried out. After reimplantation a dual antibiotic therapy was administered for usually eight weeks postoperatively.

2.4 Exclusion criteria

Patients with an incomplete data situation or negative informed consent were excluded.

2.5 Classification of periprosthetic joint infections

When an infection was present, it was classified according to the period between last implantation and onset of symptoms on the one hand and duration of symptoms on the other hand, as summarized in Table 11. In case of an acute onset of symptoms within the first three month after the prior surgery an infection was classified as acute postoperative. If more than 3 months had elapsed, infections were classified as an acute hematogenous infection. All infections with an insidious clinical course and a duration of symptoms more than 4 weeks were classified as chronic infections.

Table 11 - Criteria for classification of periprosthetic joint infection

Onset of symptoms	**within 3 months after implantation**	**more than 3 months after implantation**
Acute (< 4 weeks)	Acute postoperative	Acute hematogenous
Insidious (> 4 weeks)	Chronic	

2.6 Case definition

The diagnosis of a periprosthetic joint infection was defined as existence of at least one of the following criteria:

1. Visible purulence of a preoperative collected aspirate or intraoperative proof of infected tissue (by the surgeon).

2. Presence of a sinus tract communicating with the prosthesis.

3. Acute inflammation in intraoperative permanent tissue sections by histopathology.

4. Microbial growth in preoperative joint aspirate, intraoperative periprosthetic tissue or sonication fluid of the removed implant (>50 CFU/ml sonication fluid) or synovial fluid with >2000 leukocytes/µl or >70% granulocytes.

5. A microorganism was considered as causing pathogen, if found in culture of the synovial fluid or in periprosthetic tissue or sonication culture (considered positive if ≥50 CFU/ml).

A treatment failure was defined, when additional surgery out of septic reasons was necessary after reimplantation, as it is part of the Delphi consensus definition 2013 [122]. Treatment success was defined as an in-situ prosthesis and no further necessary surgeries out of septic reasons.

A satisfactory therapy success was defined as an in-situ prosthesis and a certain score in the follow-up surveys.

2.7 Collected data

For primary data collection and initial calculation, Excel® 2010 and 2016 (Microsoft) was used. For calculation of the Kaplan-Meier curves and for the univariate analysis, Medcalc® Version 17.6 was used.

2.7.1 From patient charts collected data

Patient data:

- Basic medical information: name, sex, date of birth, height, weight, previous operations, secondary diagnosis, immunosuppressive therapy,
- Date of admission and discharge

Characteristics of periprosthetic joint infection:

- pathogenesis:
  - intraoperative
  - hematogenous
- Duration between first occurrence of symptoms and diagnosis, duration between diagnosis and therapy

Clinical signs and symptoms of infection (upon admission and discharge)

- acute pain, redness, overheating, swelling, new occurred limited function and fever

Radiological signs of infect (conventional x-ray, MRI, CT and PET-CT):

- loosening of implants
- fracture
- effusion

Laboratory values, cytological, microbiological und histopathological signs of infect:

- Serum CRP, blood leukocyte count (upon admission and discharge)
- Joint aspirate: percentage of neutrophilic granulocytes, number of leukocytes
- microbiological findings of obtained tissue samples or aspirates
- blood cultures
- histopathologic findings of obtained tissue

Therapy (antimicrobial therapy and operative treatment):

- type, dosage, time and duration of antibiotic therapy
- type, extent and time of surgical therapy

2.7.2 Outcome analysis

- Recurrence rate of infection, in case of recurrence: time between therapy and recurrence.
- Complications and further surgeries regarding the affected joint
- Quality of life (question about further therapeutic progress and follow up

operations, Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC))

2.8 Statistical target- and evaluation criteria

The question was to analyse the epidemiology of periprosthetic joint infections and the outcome of previous therapy. Of special interest were factors affecting the outcome. Factors are the above-mentioned study parameters. For analysis of outcome, the probability of a persistent therapeutic success was used, which was estimated by means of the Kaplan-Meier method. A comparison of the survival curves of different subgroups by the means of log-rank test was performed. Additionally, the hazard ratios of the respective factors were calculated.

2.9 Ethical considerations

The study design was reviewed and approved by the ethics committee of the regional Medical Chamber. Additionally, it has been reviewed and approved by the institutional data protection officer.

3 Results

3.1 Patient collective – Basic characteristics

The primary query yielded 176 patients with an ICD-diagnosis T84.5, admitted to the orthopaedic department of “Klinikum im Friedrichshain” between 2010 and 2015. The inclusion criteria were met by 104 patients. In total 72 patients had to be excluded, as summarized in Figure 5. The most frequent reason was, that no periprosthetic joint infection, according to the stated definition, was present (29 cases; 40% of excluded patients). In 23 cases (32% of excluded patients) patients were not further treated in the hospital and in 18 cases (25% of excluded patients) no sufficient data was obtainable.

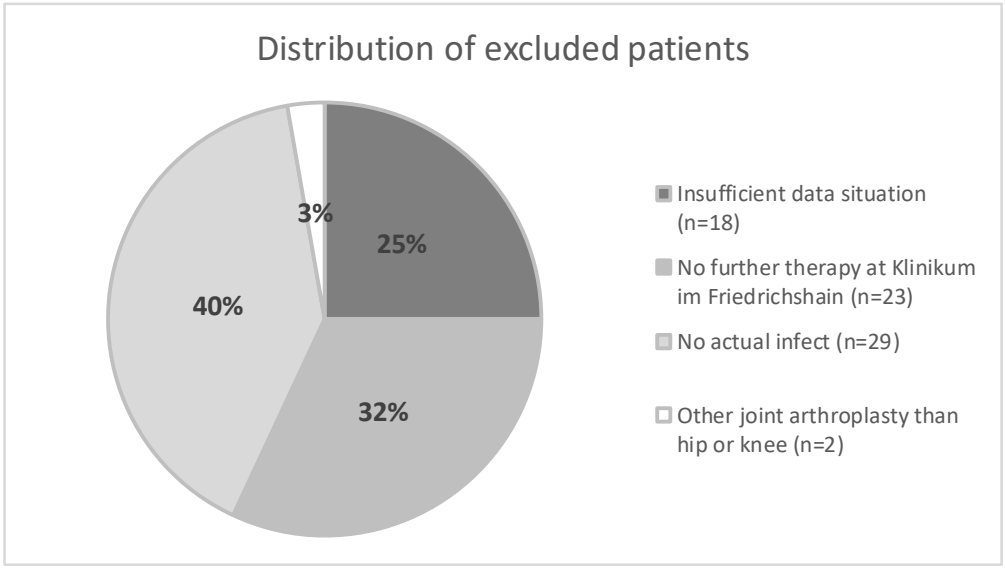


Figure 5 – Distribution of excluded patients

In Table 12, selected values describing the patient collective and the performed therapy are summarized. The median patient age was 74 years with a range from 45 to 94 years. Of 104 patients, 51 were female. Five patients deceased before completion of therapy. Mean follow-up was 25.1 months. An average of 4.3 surgical interventions (including aspiration and biopsies) had to be performed per patient. Mean duration of administered antibiotic therapy was 141.2 days.

In 58% of cases a total hip arthroplasty and in 42% of cases a total knee arthroplasty was affected. Regarding the side, 56% right and 43% left hips were found, while affected

Table 12 - Selected values of the conducted study

Number if included patients	**n=104**
Mean age in years (range):	74 (45-94)
Mean number of surgical interventions per patient (range):	4.3 (1-8)
Number of patients who finished therapy	89
Male patients	53 (50.5%)
Female patients	51 (49.5%)
Number of affected knee arthroplasties	43 (41%)
Number of affected hip arthroplasties	61 (59%)
Mean period between primary implantation and infection in months (standard deviation)	65.9 (SD=63,9)
Median period between primary implantation and infection in months (range)	44.7 (0.1 – 254)
Mean Follow-up in months (standard deviation):	25.1 (SD=10,1)
Median Follow-up in months (range):	11.7 (0-98)
Mean overall length of antibiotic therapy in days (range)	141.2 (3-597)
Number of excluded patients with ICD diagnosis T84.5	70
Frequency of clinical findings at first admission	
Sinus tract	10 (10%)
Pain	100 (97%)
Fever	10 (10%)
Redness	34 (33%)
Limited Range of motion	87 (84%)
Secretion of the wound	17 (17%)
Radiological signs of loosening at first admission	54 (52%)

knees were in 52% of cases right side and 48% left side.

3.2 Time lapse from primary implantation until infection

The majority of 67% of patients had undergone no surgeries between primary implantation and infection, while 24% have had surgeries because of an aseptic indication and 9% because of a septic indication. Mean time span from primary implantation or last previous surgery until the first intervention (aspiration or surgery) because of infection was 65.9 months, with the longest period being 21 years (254 months) and the shortest two days. The respective periods for each pathogenesis are summarized in Table 14. The shortest periods are found naturally in acute postoperative infections, ranging from two to 67 days.

Table 13 - Distribution of previous surgeries

Previous surgical interventions	
No previous surgeries (n=70)	67%
Aseptic indication (n=25)	24%
Septic indication (n=9)	9%

In acute hematogenous infections and in chronic infections, first interventions were performed after a mean duration of 74.7 and 70.2 months, respectively.

Table 14 - Period between primary implantation and first surgical intervention because of septic reasons

	Min.	Max.	Mean	Median
Acute postoperative (days)	2	67	27	14
Acute hematogenous (months)	3.0	184.9	74.7	40.1
Chronic (months)	2.3	254.3	70.2	48.2

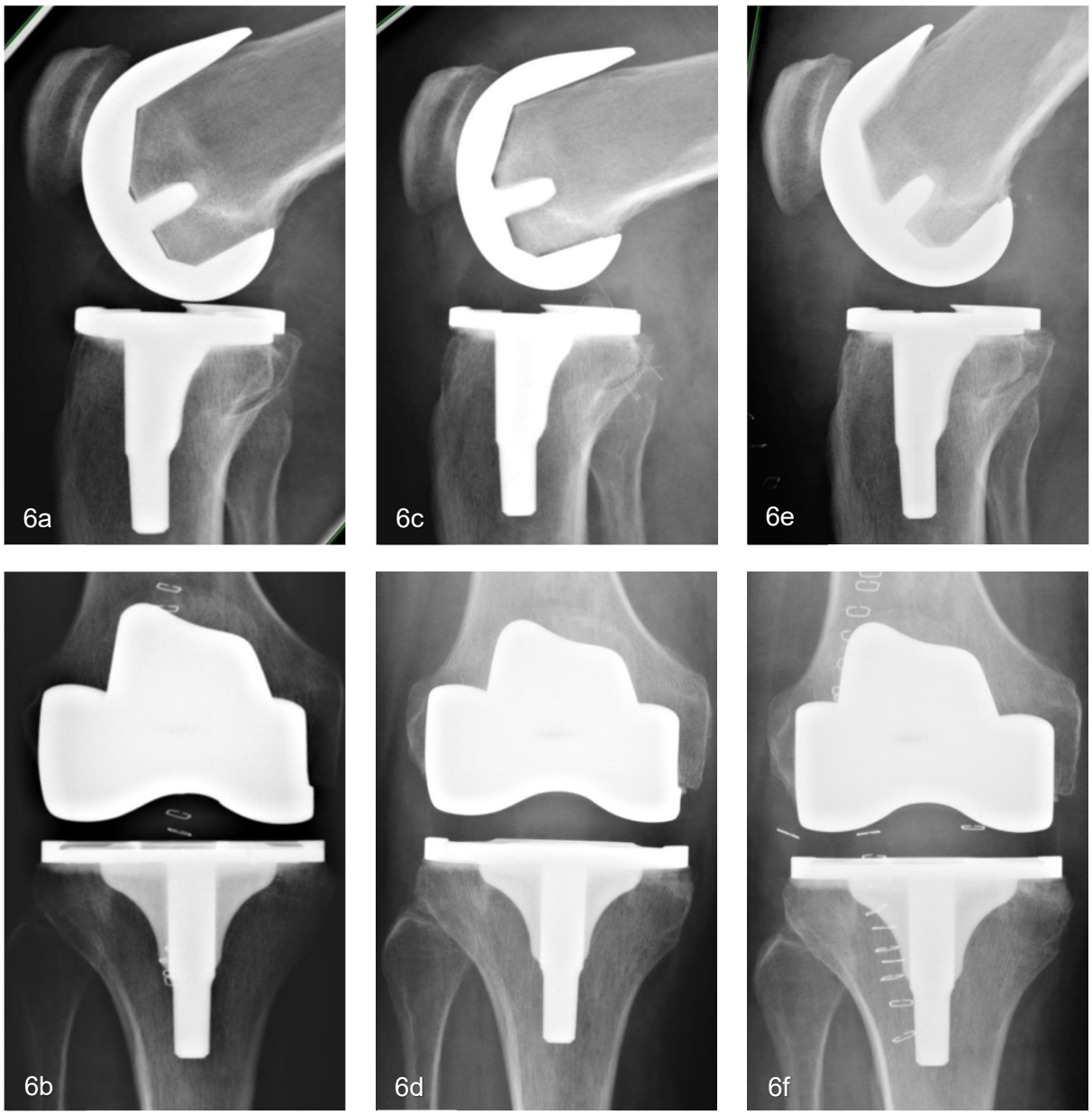


Figure 6 ***a-f*** *– Radiography in two planes of a total knee arthroplasty of the right side in a 57-year-old female patient.* ***a+b:*** *Directly after primary implantation.* ***c+d:*** *12 weeks follow-up – initial loosening of the femoral component. Staphylococcus epidermidis was identified in a single sample of a performed biopsy.* ***e+f:*** *After one-stage exchange of mobile parts and exchange of the femoral component implanted with antibiotic loaded cement combined with 8 weeks dual antibiotics.*

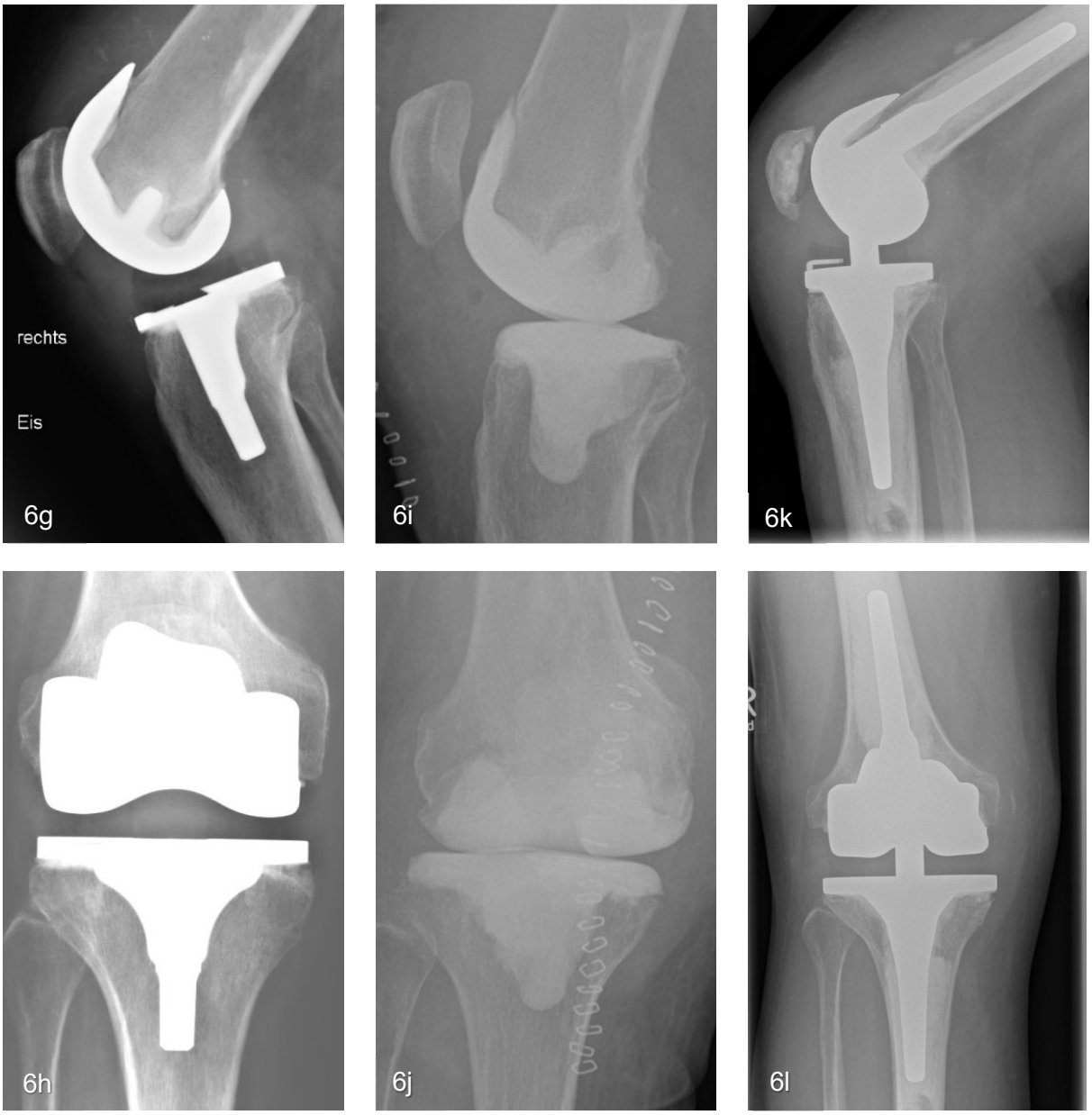


Figure 6: ***g+h:*** *6 months after one stage exchange: loosening of femoral component, osteolysis of the medial tibia.* ***i-l:*** *Two stage long-term exchange with articulating spacer for 12 weeks combined with 8 weeks dual antibiotics and reimplantation of a hinged arthroplasty.*

In Figure 6 an exemplary course of an infection of a total knee arthroplasty in a 57-year-old female patient is depicted by means of the respective radiography in two planes, which suffered constant pain from the implantation on. No redness or swelling were present. Laboratory chemical examinations were inconspicuous. *Staphylococcus epidermidis* was isolated in a single sample of a performed biopsy 12 weeks after implantation, shortly after a questionable initial loosening of the femoral component was found. A one-stage exchange of mobile parts and of the femoral component to a

cemented variant with antibiotic-loaded cement combined with 8 weeks of administration of cefuroxime and rifampicin were performed. Microbial and histopathological examination of intraoperatively collected samples yielded negative results. Postoperatively, the patient suffered persistent pain. Follow-up radiography 6 months later detected further loosening of the femoral component, an again performed biopsy yielded negative results. A two-stage long-interval exchange was performed. Histopathological findings were positive this time, while isolation of a causing pathogen by conventional cultural methods was not possible. After 12 weeks of an articulating spacer in situ combined with 8 weeks of dual antibiotics, a hinged endoprosthesis was re-implanted, after a biopsy yielded negative histopathological and microbial results. Another 8 weeks of dual antibiotics were administered postoperatively. By microbial examination of tissue samples collected during reimplantation, isolation of *Staphylococcus epidermidis* was possible. No further surgeries out of septic reasons were necessary. Of note, the questionable false-negative microbial findings of the during first and second exchange surgery as well as during the second biopsy collected tissue samples.

3.3 Type of periprosthetic joint infection

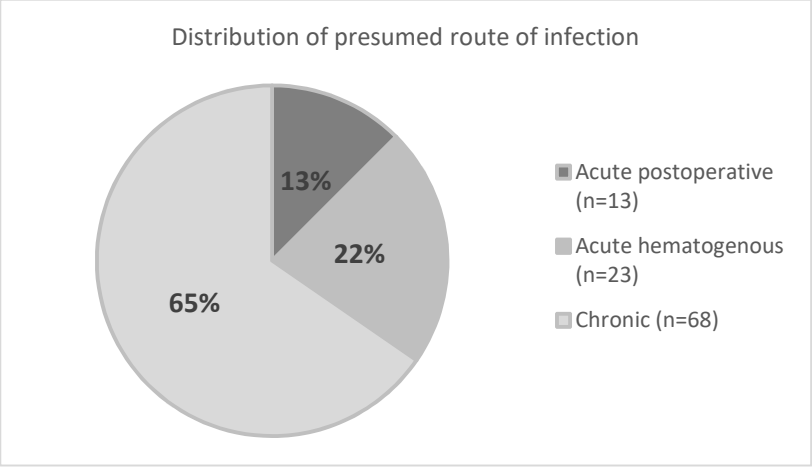


Figure 7 - Distribution of presumed route of infection

The period between primary implantation and onset of symptoms on the one hand, and the duration of symptoms on the other hand, are important factor for classification of the presumed route of infection. In Figure 7, the proportional distribution of the presumed route of infection is depicted. The most infections were chronic, with 66% of cases while the least frequent was acute-postoperative with 12% of cases.

3.4 Microbial findings

Table 15 - Microbial spectrum of isolated pathogens

Microorganism	Frequency (%)
Coagulase-negative staphylococci (n=112)	38%
Staphylococcus aureus (n=43)	15%
Streptococci (n=30)	10%
Enterococci (n=12)	4%
Gram-negative bacilli (n=13)	4%
Anaerobes(n=23)	8%
Candida spp.(n=4)	1%
Polymicrobial(n=17)	6%
Unknown (culture false-negative) (n=27)	9%
Other(n=13)	4%

In Table 15 the distribution of overall isolated pathogens in the analysed patient collective throughout the course of the treatment is summarized. The most frequent pathogens found were coagulase-negative staphylococci and *Staphylococcus aureus*. In the group of *Staphylococcus aureus*, 7 (16%) were classified as methicillin-resistant *Staphylococcus aureus* (MRSA). This corresponds to 2.4% of the overall identified pathogens.

In the conducted study, a large proportion of contradictory microbial results of aspiration and biopsy in comparison to the first surgery was found. The continuity of microbial findings in terms of a positive or negative finding is depicted in Figure 8. In comparison to the microbial findings of the first surgery, 68% (34 cases) of the performed aspirations and 61% (14 cases) of the performed biopsies were either concordant positive or negative.

When analysing the respective positive results, discordant positive results with contradictory identified pathogens are of matter. In the group, in which the performed aspiration and the following surgery were both positive, out of 33 cases in 21% (7 cases) different pathogens have been identified. Concerning the biopsy this share was higher, with 45% (5 out of 11 cases) showing different positive results. Additional results are summarized in Table 16.

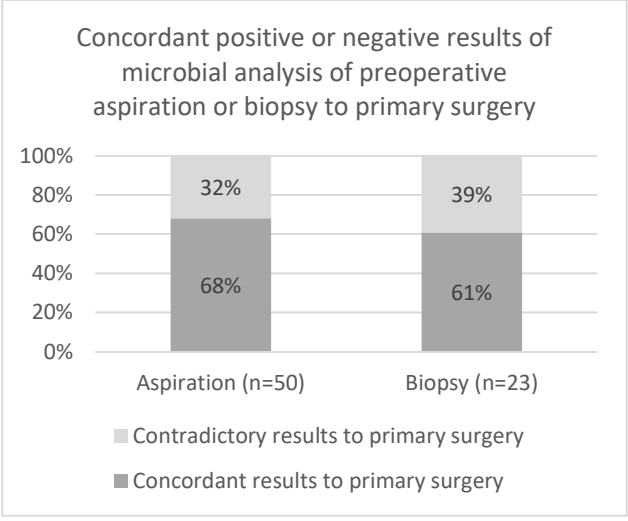


Figure 8 - Concordant positive or negative results of microbial analysis of preoperative aspiration or biopsy to primary surgery.

Table 16 - Microbial results of preoperative aspiration and biopsy compared to primary surgery

Microbial results of preoperative diagnostics compared to primary surgery

Aspiration				**Biopsy**			
	Surgery positive	**Surgery negative**	**overall**		**Surgery positive**	**Surgery negative**	**overall**
Aspiration positive	**33**	**10**	*43*	**Biopsy positive**	**11**	**6**	*17*
Aspiration negative	**6**	**1**	*7*	**Biopsy negative**	**3**	**3**	*6*
overall	*39*	*11*	*50*	**overall**	*14*	*9*	*23*
Number of discordant positive results	**7**				**5**		

Given the assumption, that all treated patients had an infection by the definition stated in chapter 2.6, these values result in a sensitivity of 86.0% (95% Confidence interval: 73.3% to 94.2%) concerning the aspiration and 73.9% (95% Confidence interval: 51.6% to 89.8%) concerning the biopsy. The specificity is not applicable, since patients without infection were excluded by the design of the study.

3.5 Concordance of microbial findings

The concordance of the microbial and histopathologic results of the initial biopsy and of the primary surgery, respectively, is depicted in Figure 9. Only cases, in which both histopathologic and microbial results were available, are considered. Of all cases, that yielded positive histopathologic results in the initial biopsy, a pathogen was identified in 44% of cases, where as in all cases with negative histopathologic findings the microbial findings were concomitant negative in 27% of cases. Concerning the primary surgery,

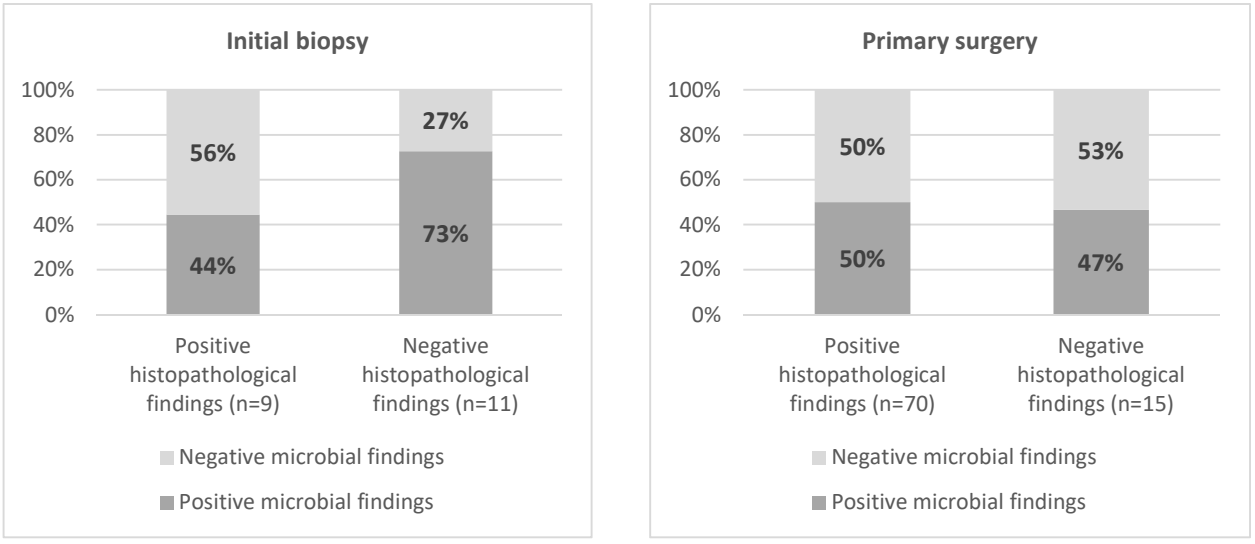


Figure 9 - Concordance of microbial and histopathologic results of the initial biopsy (left) and primary surgical intervention (right)

this distribution changes. Out of all cases of positive histopathologic findings, the microbial results were in 50% concomitantly positive, while in 53% of cases of negative histopathological findings, they were concomitant negative.

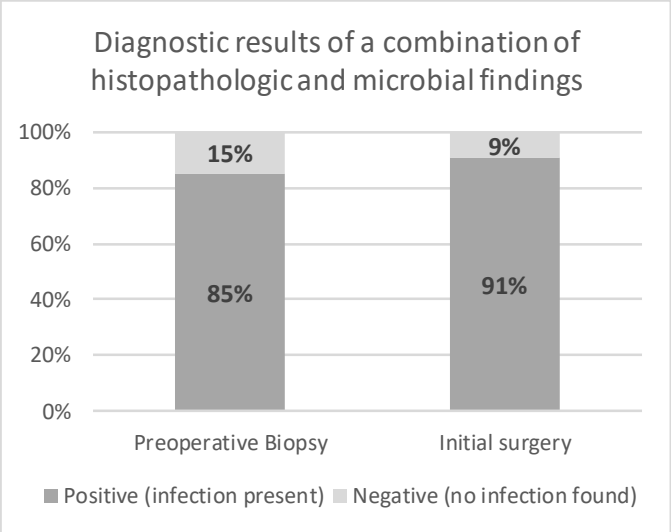


Figure 10 - Diagnostic results of a combination of histopathologic and microbial findings

The diagnostic results of a combination of microbial and histopathologic findings is depicted in Figure 10. Again, only cases with available histopathologic and microbial findings were considered. The sensitivity concerning the biopsy was 85% (95% confidence interval: 62.1% to 96.8%) and concerning the initial surgery it was 90,6% (95% confidence interval: 82,3% to 95,9%).

3.6 Chosen regimen of therapy

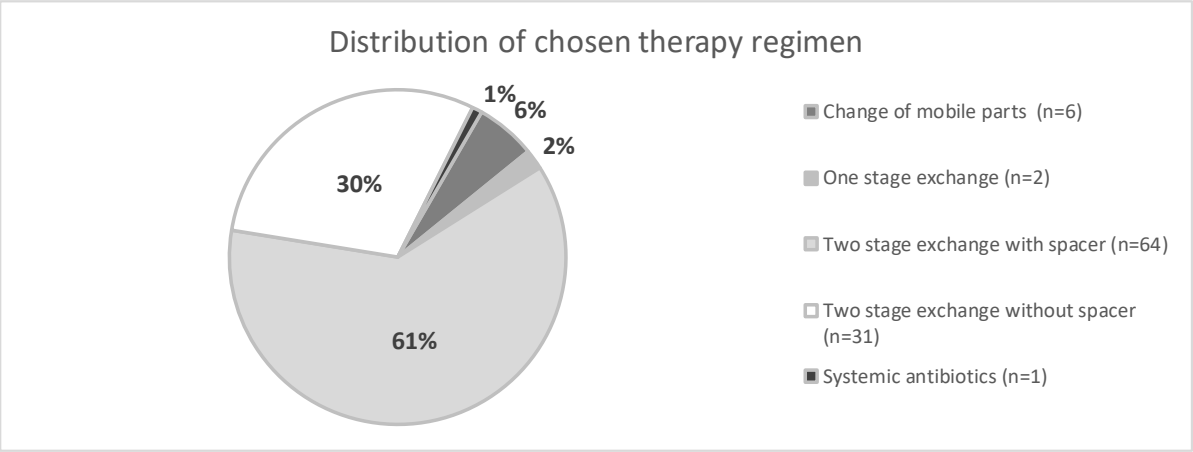


Figure 11 - Distribution of chosen therapy regimen

The strategy of the therapy of periprosthetic joint infections depends on the presumed route of infection and the intervals of time between primary implantation of the arthroplasty, onset of symptoms and begin of the therapy. The proportional distribution of the performed therapy is depicted above, in Figure 11. In this study, in general a two-staged, long-term prosthesis exchange was deemed to be necessary, being performed in over 90 percent of cases. One-stage exchange and change of mobile parts were only

performed in a minority of cases. In one case, a surgical therapy after diagnostic biopsy was rejected by the patient and only systemic antibiotics were administered. In Figure 12, an exemplary course of a chronic postoperative infection of a total hip arthroplasty in a 69-year-old patient, treated by a two-stage exchange, is depicted. The patient suffered 11 months after implantation progredient pain of the hip, an initial loosening of the femoral component was found by radiography. Microbial examination after aspiration identified *Staphylococcus epidermidis* as causing pathogen.

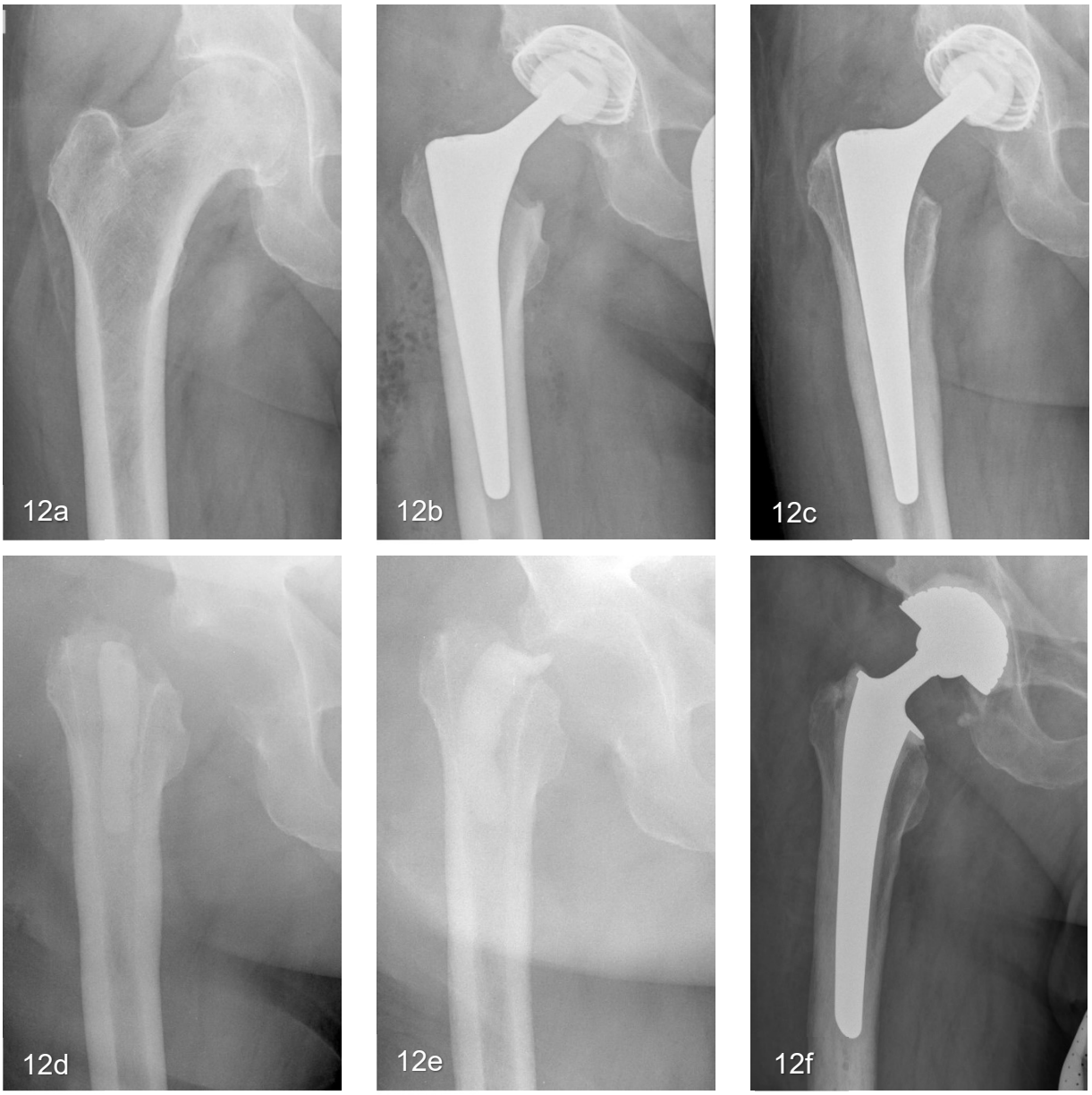


Figure 12 ***a-f****: Radiography of total hip arthroplasty in a 69-year-old patient.* ***a:*** *Before implantation.* ***b:*** *After implantation.* ***c:****11 months after implantation, loosening of the femoral component.* ***d:*** *After explantation, monobloc spacer in situ.* ***e:*** *After spacer exchange because of isolation of Cutibacterium by a biopsy after 10 weeks of spacer in situ.* ***f:*** *After reimplantation of a cemented total-hip arthroplasty.*

A two-stage long term exchange with implantation of an antibiotic loaded bone cement spacer, alongside with 8 weeks dual-antibiotics, was performed. *Staphylococcus*

epidermidis was isolated again in the samples collected during explantation of the endoprosthesis. After 10 weeks, a biopsy, which resulted in isolation of *Cutibacterium* (formerly known as *Propionibacterium*) spp., was performed. Therefore, an exchange of the spacer and irrigation and debridement of the joint were performed. Dual antibiotics were administered for another 8 weeks. After 10 weeks, a biopsy yielded negative histopathological and microbial findings and reimplantation of a cemented endoprosthesis was possible.

3.7 Infection control after initial explantation in two-stage exchange

The rate of infection control after the initial septic revision in two-stage exchange protocols depending on the joint is depicted in Figure 13. As in all cases of infected knee-arthroplasties a spacer was used, there is only one group regarding total knee arthroplasties depicted. Infected Hip arthroplasties treated with a spacer were found to have a superior rate of initial infection control of 87%, while infected knee arthroplasties treated with a spacer showed an inferior initial infection control rate of 76%, comparable to that of infected hip arthroplasties treated without a temporary spacer, which was 74%.

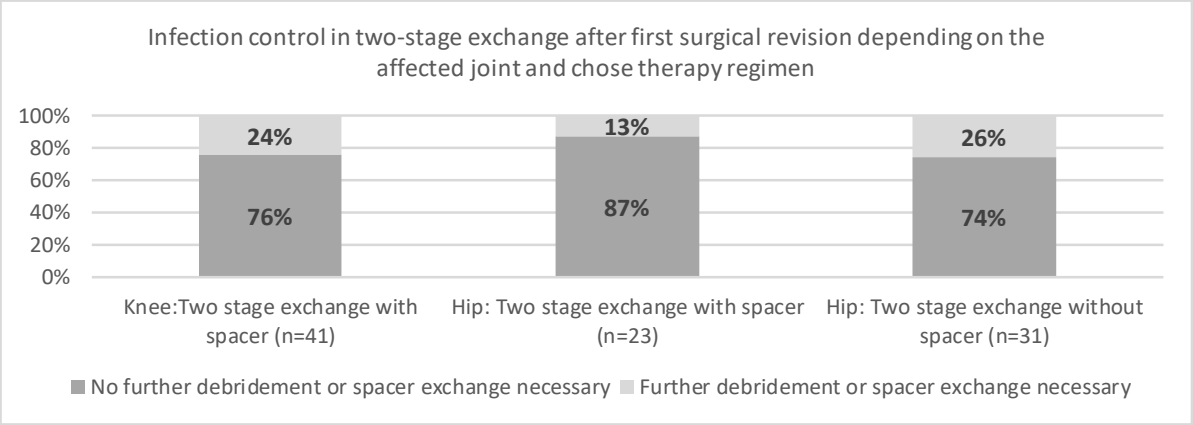


Figure 13 - Infection control after first surgical revision in two-stage exchange depending on joint and use of a temporary spacer

In Figure 14 the rate of initial infection control depending on the presumed pathogenesis is depicted. The highest rate of 80% of infection control by the initial treatment was achieved in patients suffering chronic infection, while in acute hematogenous infections this value was 74%. In acute postoperative infections treated with a two-stage exchange, the initial revision surgery was successful in 71%. Of note, that this group consists of seven patients, since most of the performed one-stage exchanges in the present study have been performed in this group, which are not included in this diagram. The latter ones

will be discussed below.

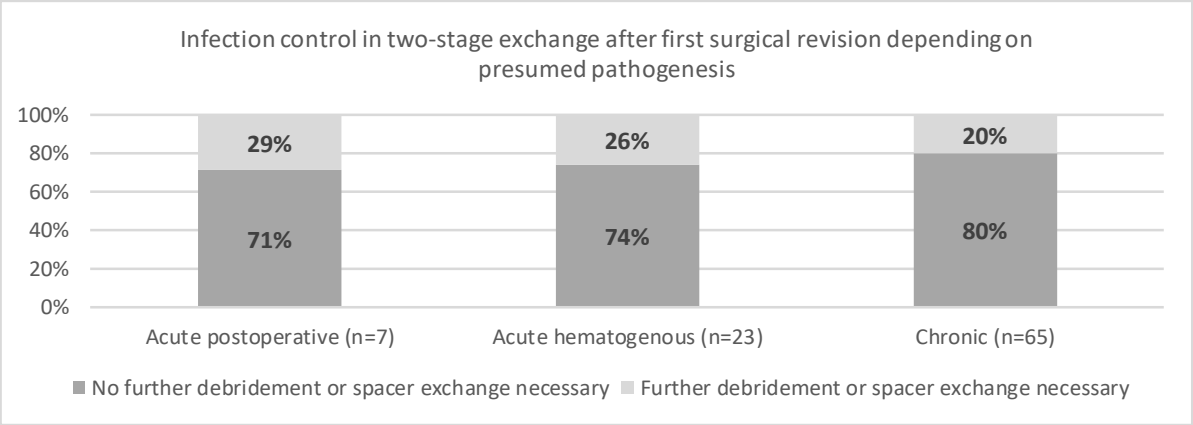


Figure 14 - Infection control after first surgical revision in two-stage exchange depending on presumed pathogenesis

3.8 Infection control after finished treatment

The necessity of any further surgical treatment after reimplantation out of septic reasons is an important factor, as it is part of the definition of the Delphi-based International Multidisciplinary Consensus from 2013 [122]. In the following, this issue is referred to as infection control and is below depicted depending on different factors.

In Figure 15 the frequency of additional surgeries out of septic reasons after performed reimplantation is depicted. In 66% of cases no further surgeries had to be performed, while in 17% of patients had to undergo further surgery. In 11% of cases no attempt of reimplantation was performed and 6% of patients deceased before reimplantation.

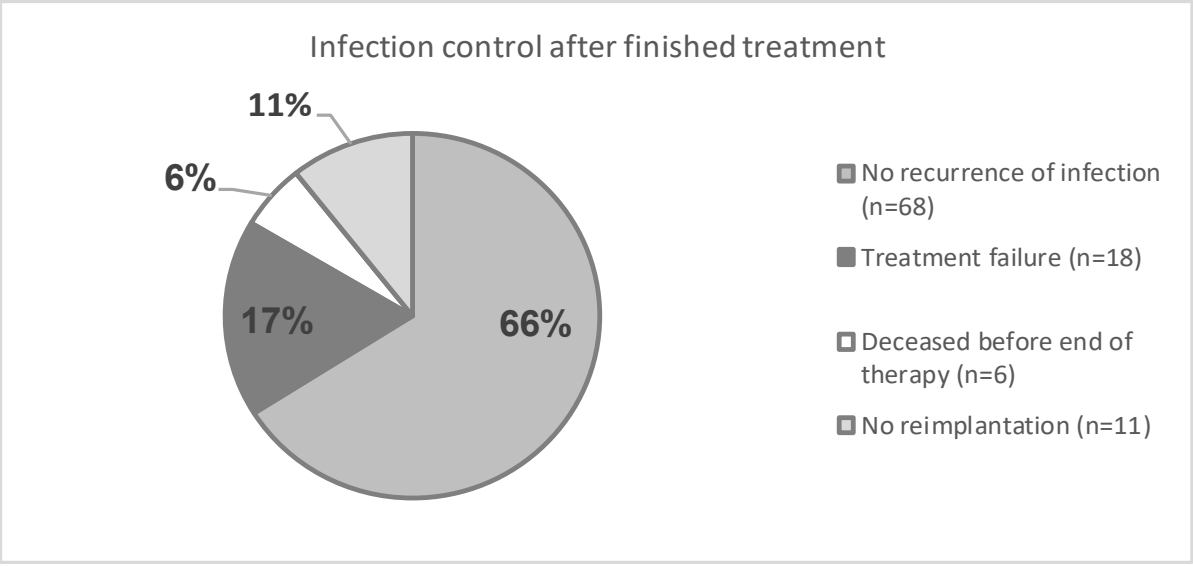


Figure 15 - Overall necessity of further surgical treatment

The rate of infection control overall and depending on the chosen therapy regimen is depicted in Figure 16. Patients, who did not undergo reimplantation, are not considered. If subdivided according to the chosen therapy regimen, the lowest percentage of further necessary surgical interventions of 20% has been found, when a two-stage revision with spacer in infected hip arthroplasties has been performed. Change of mobile parts was the least successful strategy with an achieved infection control in 40% of cases. Change of mobile parts and one-stage exchange were both performed in less than ten cases. Therefore, a statistical analysis is not appropriate.

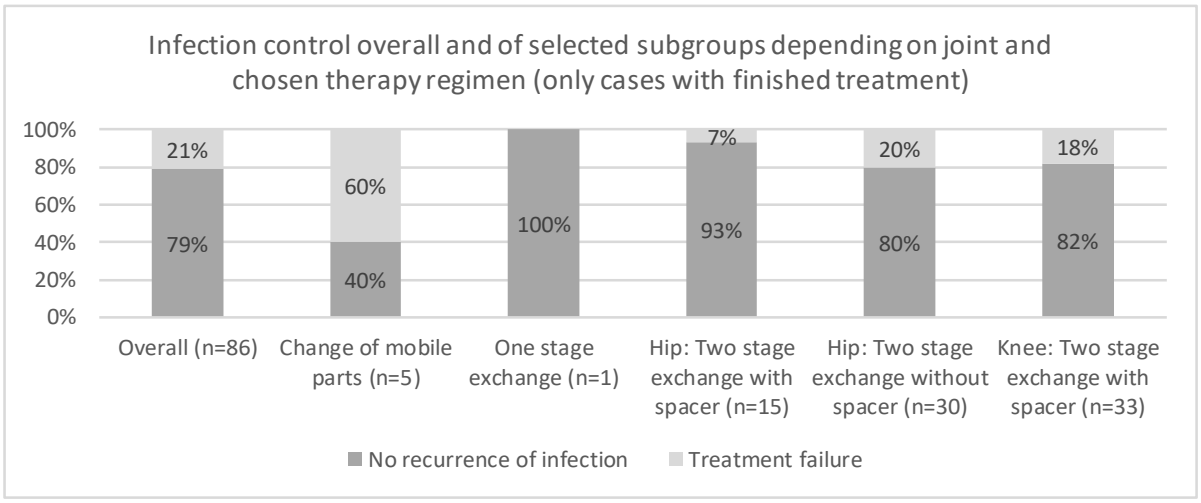


Figure 16 - Necessity of further surgical treatment depending on chosen therapy regimen

In Figure 17, different groups of presumed pathogeneses are depicted with the respective rate of infection control. Patients with chronic hematogenous infections had no further surgeries to undergo in 73% of cases, while, in contrast to that, in patients with acute-postoperative infections additional surgeries had to be performed in 64%.

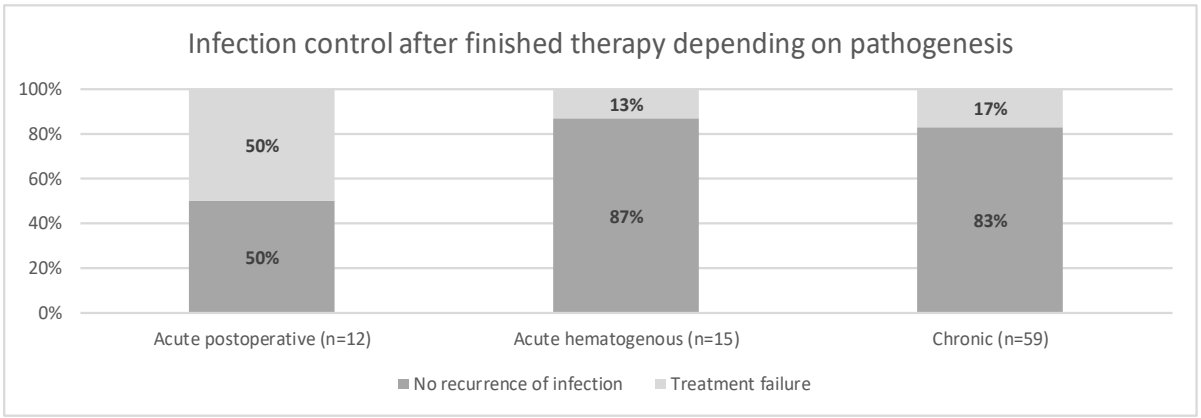


Figure 17 - Necessity of further surgical treatment according to presumed pathogenesis (only patients who finished treatment)

3.8.1 Antibiotic therapy

As stated above, mean overall duration of antibiotic therapy was 141 days. The overall distribution of prescribed antibiotics is summarized in Table 17. The most frequently used antibiotic agent was Cefuroxime, which was used in 25% of cases, followed by Clindamycin in 17% of cases.

Table 17 - Overall frequency of used antibiotics

Antibiotic	Frequency of use
Cefuroxime	25%
Clindamycin	17%
Rifampicin	11%
Ciprofloxacin	9%
Vancomycin	9%
Ampicillin/Sulbactam	8%
Linezolid	3%
Cotrimoxazole	3%
Other	6%

After reimplantation, the use of biofilm-active antibiotics like rifampicin [45] or quinolones [94] has been shown to be an important factor. In Figure 18, the rate of infection control is depicted regarding whether a biofilm-active antibiotic therapy has been administered after reimplantation. In the observed patient-collective biofilm-active antibiotics have been used in the minority of treatment regimens (27 cases or 31%) after reimplantation. In this group 16% of patients had to undergo additional surgeries out of septic reason compared to 22%, when no biofilm-active antibiotics where used.

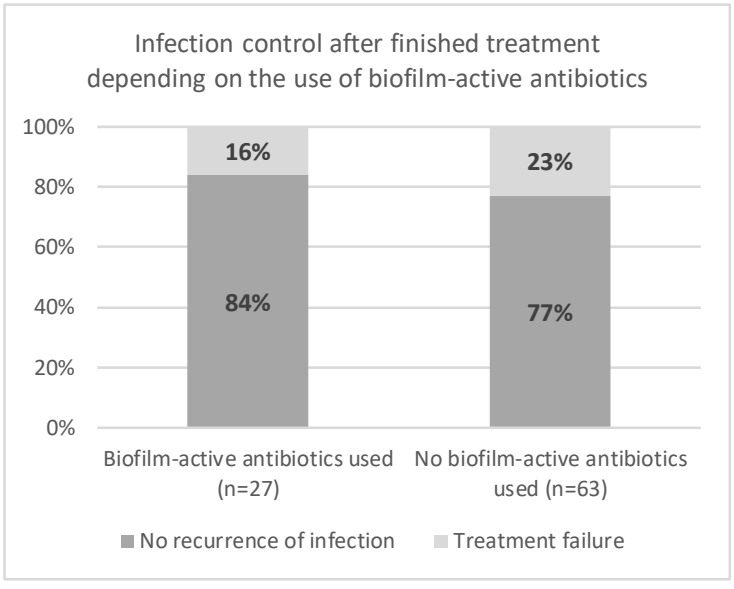


Figure 18 - Proportion of use of biofilm-active antibiotics and necessity of further surgical treatment (only patients who finished treatment)

In Figure 19, the rate of infection control in the subgroups of different pathogenesis is depicted depending on the use of biofilm-active antibiotics. Both, the group of patients with acute postoperative and acute hematogenous infections, are rather small compared to the group of patients with chronic infections. Of the patients with acute postoperative infections, all three treated with biofilm-active antibiotics had no recurrence of infection, while an infection control was achieved in only three out of nine cases, when using no biofilm-active antibiotics. In the group of

patients with chronic infections, the ratio was balanced, while in the group of acute

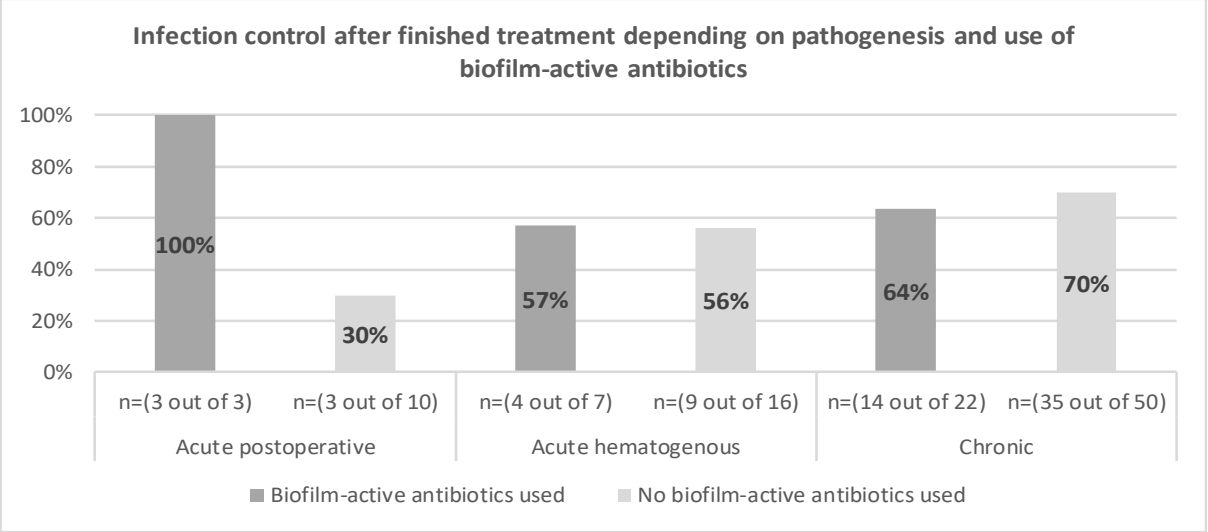


Figure 19 - Rate of infection control in different subgroups depending on pathogenesis and use of biofilm-active antibiotics

hematogenous infections the rate of infection control was lower, when biofilm-active antibiotics were used. The restriction must be made, that the mentioned small numbers yield no valid statistical data.

3.8.2 Causing pathogen

In Figure 20, this number is depicted depending on the pathogen being identified either by pre-operative aspiration or biopsy, respectively, or by the tissue samples obtained in the first septic surgery. In case of discordant microbial results, the classification was based on the pathogen isolated by the tissue samples of the first revision.

By numbers, the four most frequently found pathogens were: coagulase-negative staphylococci (32 patients), *Staphylococcus aureus* (15 patients), streptococci (12 patients) and culture false-negative (17 patients). The most favourable ratio of infection control to treatment failures was found in the group of infections caused by an unknown pathogen (88% vs. 12%). The highest rate of patients deceased in course of the treatment as well as patients who did not finish the treatment, was found in the group of infections caused by *Staphylococcus aureus*.

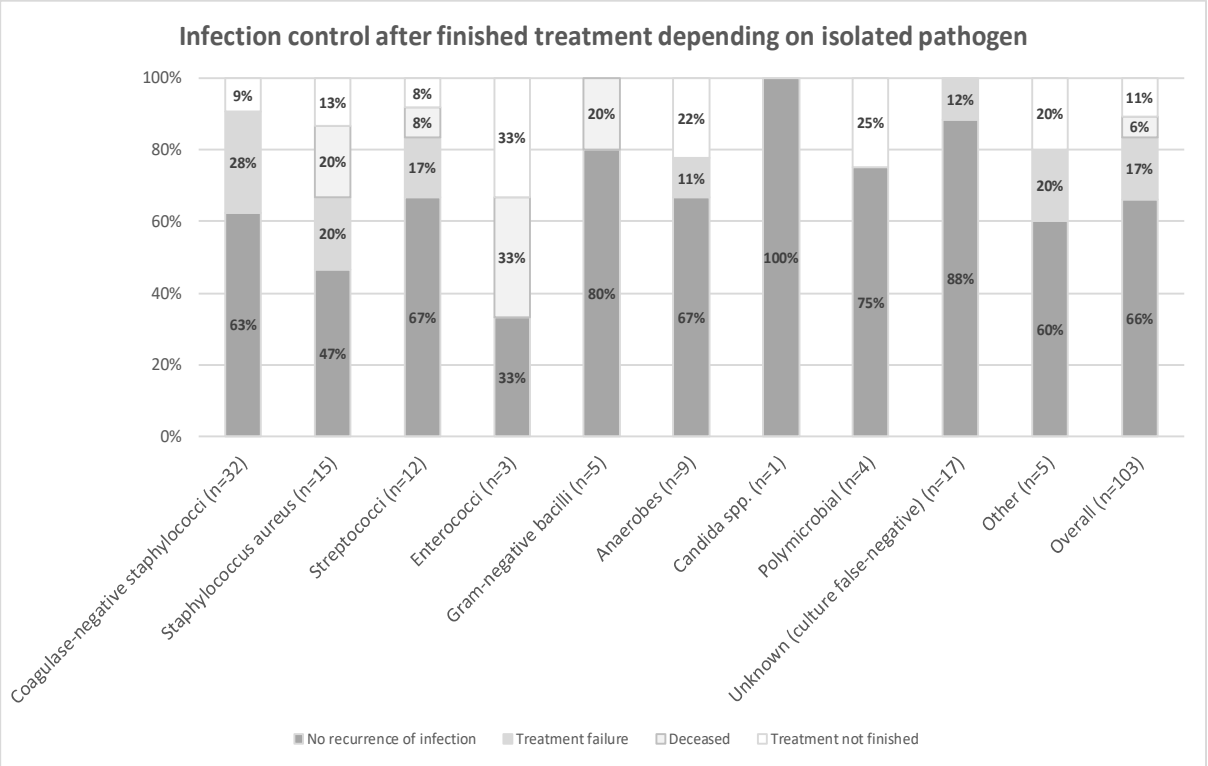


Figure 20 - Necessity of further surgical treatment depending on the pathogen identified by the time of first septic surgery

3.9 Survival Analysis

The following Kaplan-Meier survival analyses are conducted based on the rate of infection control, therefore any further surgery out of septic reasons and any reinfection of the same joint after re-implantation were defined as end-point. Deceased patients, cases in which no reimplantation was performed and lost-to-follow-up were defined as censored cases. This entails, that in contrast to the diagrams concerning the rate of infection control, also patient without finished treatment are included. Therefore, numbers may differ. The Kaplan-Meier curve of the overall study population, is depicted in Figure 21.

A mean survival of 4.97 years (standard error 0.3) and a 95% confidence interval from 4.3 to 5.6 was found. Most of treatment failures occurred within the first year after treatment with a number at risk after one year of 43 patients. In the second year the large part of the remaining treatment failures occurred. The Kaplan-Meier analysis of the comparison of the treatment of infected knee and hips is depicted in Figure 22. As mentioned above concerning the overall Kaplan-Meier curve, most of treatment failures occurs in year one and two, respectively. There was no major difference of infection control between infected

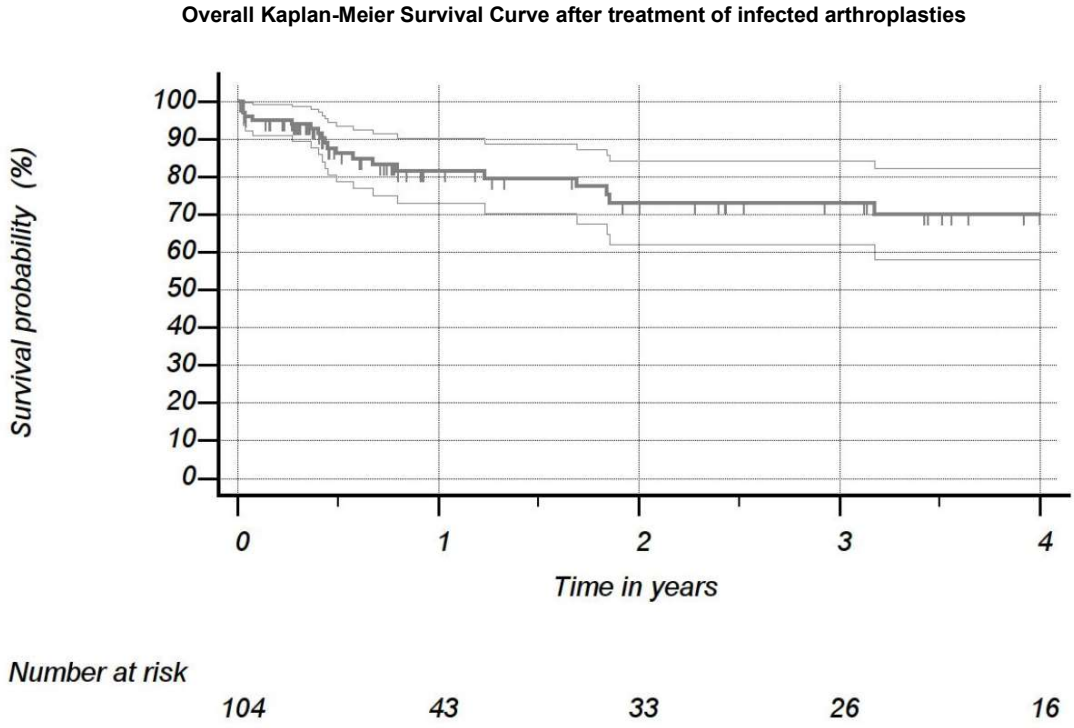


Figure 21 - Overall Kaplan Meier Survival Curve with key values after treatment of infected arthroplasties

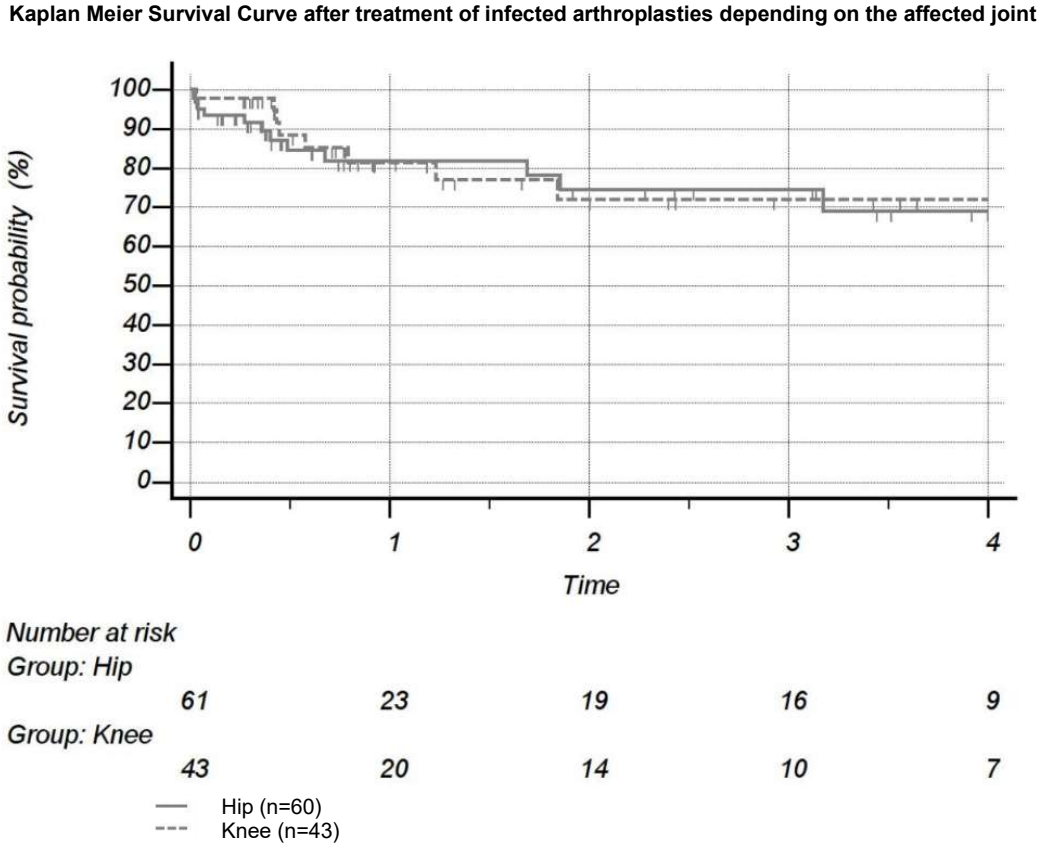


Figure 22 - Kaplan Meier curve after treatment of infected hip and knee arthroplasties

Kaplan Meier Survival Curve after treatment of infected arthroplasties depending on the presumed pathogenesis

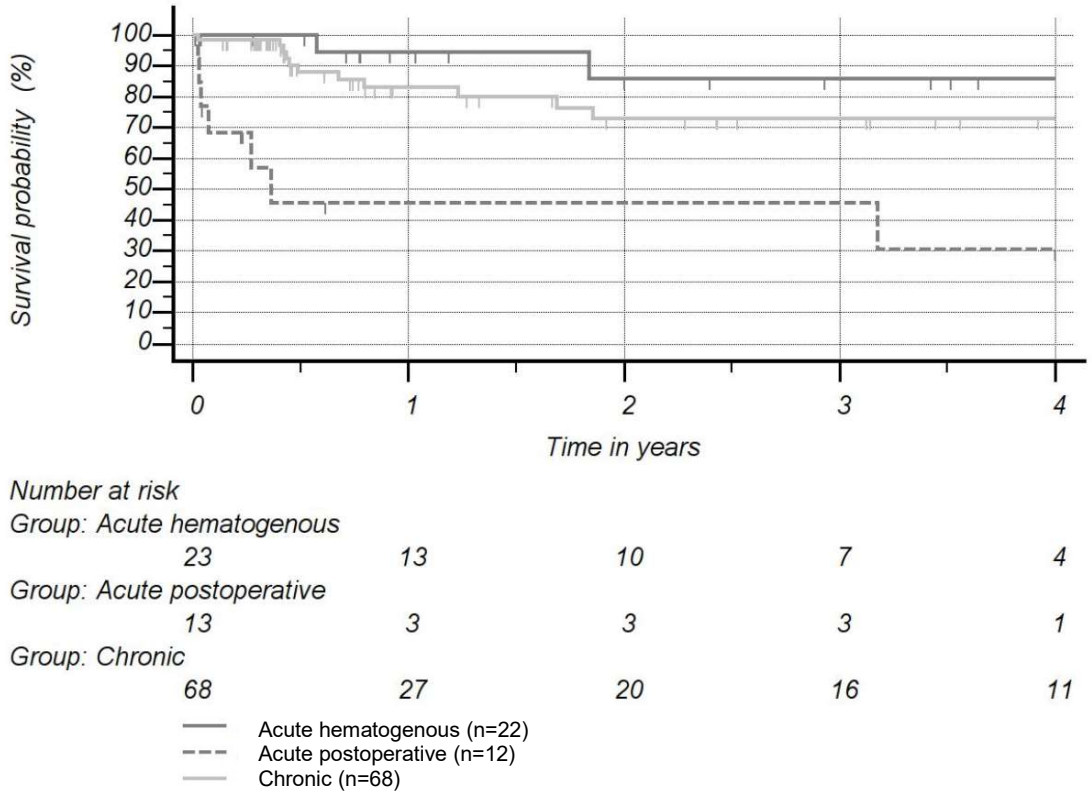


Figure 23 - Kaplan Meier Survival curve after treatment of infected arthroplasties depending on presumed pathogenesis of infection

Kaplan Meier Survival Curve after treatment of infected hip arthroplasties depending on the use of a spacer

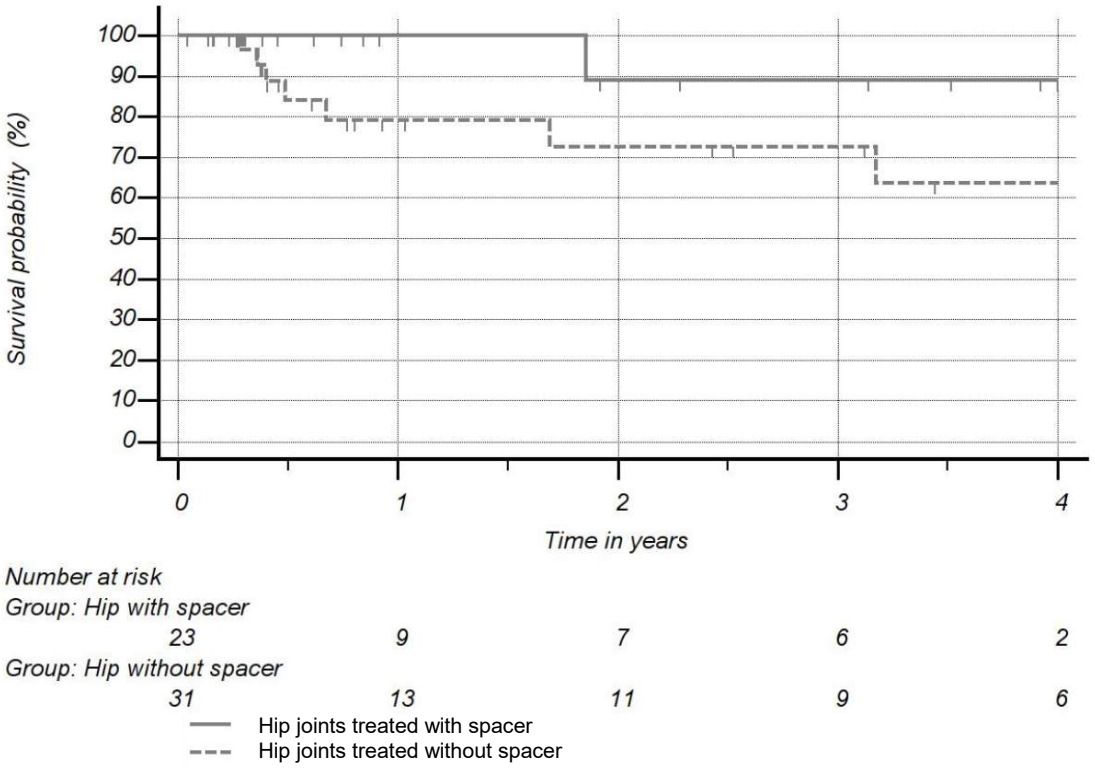


Figure 24 - Kaplan Meier curve after treatment of infected hip arthroplasties depending use of a spacer

hip and knee arthroplasties found. This is reflected in the log-rank test, which shows no significant differences with a Chi-squared=0.088 and p=0.767. In Figure 23, the Kaplan Meier curve depending on the presumed pathogenesis is depicted. In the acute post-operative group, especially in the first year relatively more treatment failures than in the other groups are found. The log-rank test shows significant difference of the groups, with a chi-squared=20.295 and p <0.0001.

In Figure 24, the Kaplan-Meier curves in the first four years of hip joints treated with and without spacer are depicted. The group treated with spacers shows less treatment failure, especially in the first year. As already found regarding the rate of infection control after reimplantation, the outcome of infected hip arthroplasties treated without spacer is inferior compared to the use of a spacer. This effect reaches no statistical significance, as the log-rank test results in a chi-squared=2.755 and p=0.098. Of note, that in the group treated with spacer, less patients have undergone reimplantation.

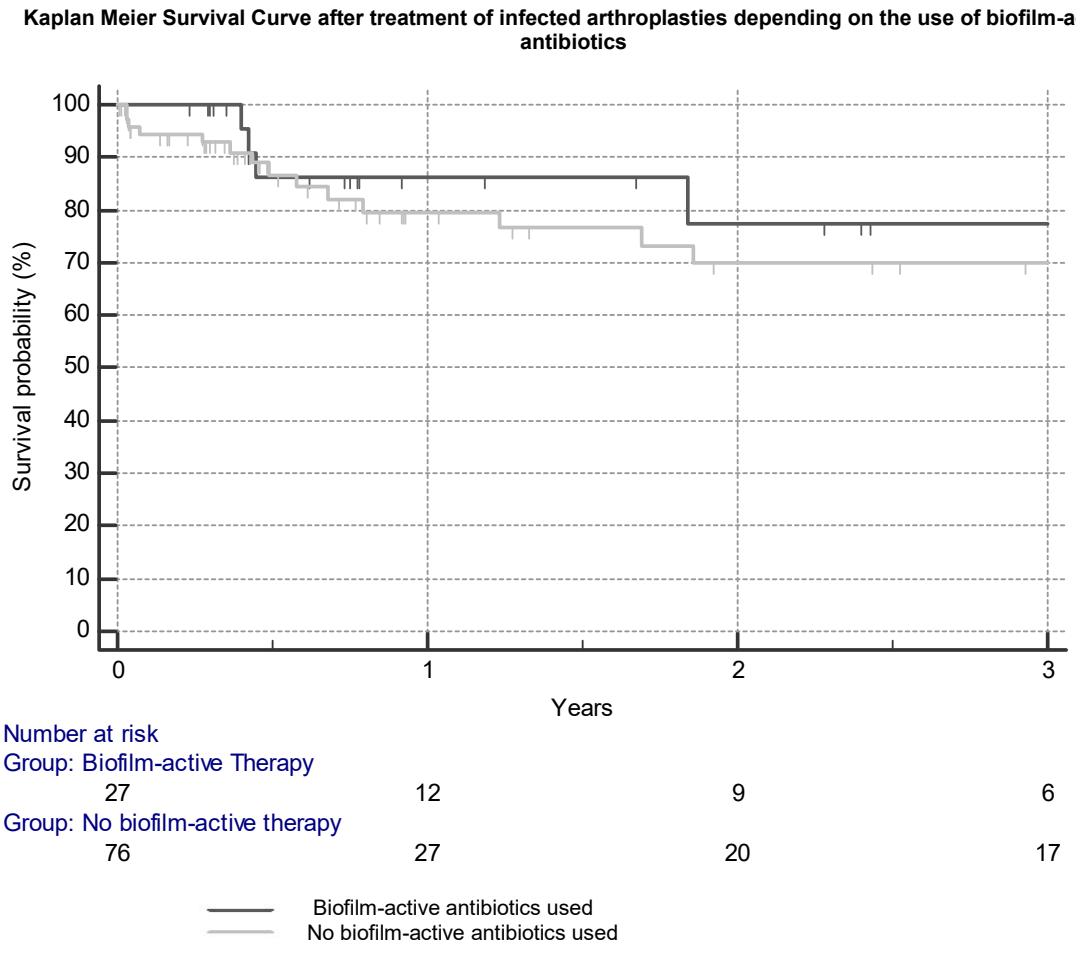


Figure 25- Kaplan Meier Survival curve depending on the use of biofilm-active antibiotics

In Figure 25, the Kaplan-Meier curve depending on the use of biofilm-active antibiotics is depicted. As stated in chapter 3.8.1, the group treated with biofilm-active antibiotics shows relatively more treatment failures, but this effect reaches no significance in the log-rank test with Chi-squared=0.86 and p=0.354.

3.10 Hazard ratios

The hazard ratios for further necessary treatment out of septic reasons of the above analysed factors are summarized in Table 18 and Table 19. Statistical significant difference in outcome was found only in comparison of the different presumed pathogeneses with p<0.0001. The comparison of the other groups showed no significance. Though, the use of a spacer in infected hip arthroplasties seems superior, as the hazard ratio was 4.93 and p=0.098 for patients with no spacer used compared to the group of patients treated with spacer.

Table 18 - Hazard ratio with 95% confidence interval of different factors

Factor	Hazard ratio (95% Confidence interval)	P Value
Knee (vs. hip)	0.87 (0.36 to 2.12)	0.767
No biofilm-active antibiotics used	1.51 (0.55 to 4.13)	0.466
No spacer used (hips)	4.93 (1.21 to 20.13)	0.098

Table 19 - Hazard ratio with 95% confidence interval of different pathogeneses, p<0.0001

Factor	Acute hematogenous	Acute postoperative	Chronic
Acute hematogenous	-	11.31 (1.95 to 65.40)	2.22 (0.81 to 6.09)
Acute postoperative	0.09 (0.02 to 0.51)	-	0.196 (0.04 to 1.00)
Chronic	0.45 (0.16 to 1.24)	5.10 (1.00 to 25.96)	-

3.11 Follow-up survey and functional outcome

As listed in Table 20, of overall 52 patients a response was received. In some cases of deceased patients, the dependants answered. This corresponds to an overall follow-up rate of 53% of patients not deceased before end of therapy. The patients were asked how much analgesics they take regularly. The results are depicted in Figure 26. The majority of 76% of participants of the survey took at time of follow-up either no or non-opioid analgesics only.

Table 20 - Distribution of participation in the follow-up survey

Number of answers	**52**	
Included surveys	37	71%
Refusal to participate	7	13%
Deceased	8	15%
Overall follow-up rate		53%

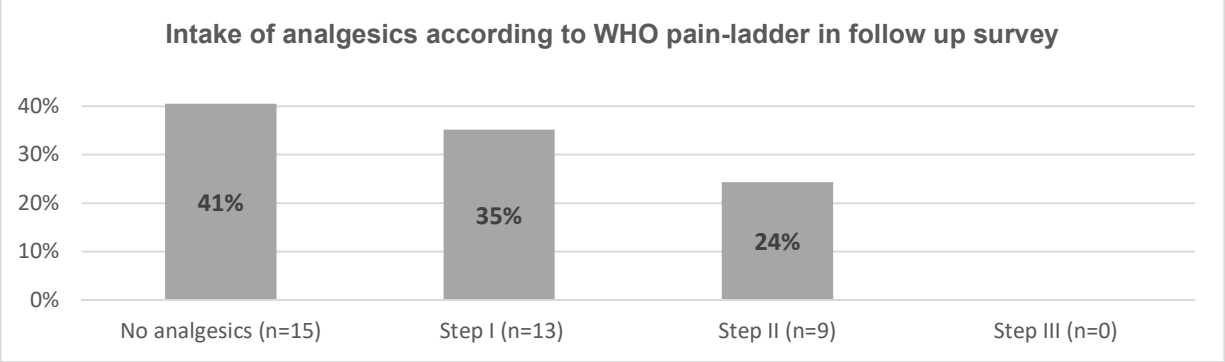


Figure 26 - Intake of analgesics according to WHO pain ladder in follow up survey

Furthermore, the patients were asked to fill out a WOMAC-Form [121]. Categories of the WOMAC questionnaire are pain (five questions), stiffness (two questions) and functional limitation (17 questions). Each question can be answered by five options, ranging from “none”, equalling zero points, to “extreme”, equalling four points, resulting in a possible overall Score of 96 points. A lower Score equals less complaints. When regarding the respective categories, due to different number of questions per category, the mean number of points per question is more informative than the overall mean value of a single category. The results of the WOMAC follow-up survey are denoted in Table 21. Concomitant to the distribution of analgesic intake, the mean pain score was 0.9 of 4 possible points per question. In the category “Stiffness” this value was 1.6 and in the category “Function” it was 2.1.

Table 21 - Results of WOMAC follow-up survey

	Pain (max. 20)	Stiffness (max. 8)	Function (max. 68)	Overall (max. 96)
Mean	4.5	3.1	27.9	37.3
Mean per question	0.9	1.6	2.1	1.8
Standard deviation	1.1	1.5	1.5	1.5
Min	0	0	0	0
Max	14	8	64	84
Median	3	3	26	36

In Table 22, the results of questions regarding the use of walking aids, the ability to ascend or descend stairs and the ability to walk are denoted. Most respondents (70%) report the affected joint to be stable. A relatively big share of 40.5% of patients uses walkers or axillary crutches for walking. Ascending and descending stairs is possible with using the handrail only for the majority of 78.4% of patients. Roughly half of respondents (55%) can walk 500 metres or more, while the other half is limited to distances below 500 metres or tied to the house.

Table 22 - Results of outcome survey regarding use of walking aids, ability to climb stairs and ability to walk

Patients who reported the affected joint to be stable	26 (70.2%)
Use of walking aids	
No walking aid used	9 (24.3%)
One crutch	8 (21.6%)
Two crutches	2 (5.4%)
Walker or axillary crutches	15 (40.5%)
Stair climbing	
Ascending and descending stairs without help	2 (5.4%)
Descending stairs with handrail only	1 (2.7%)
Ascending and descending stairs with handrail only	29 (78.4%)
Ascending stairs with handrail, descending impossible	2 (5.4%)
Ascending and descending not possible	3 (8.1%)
Ability to walk	
No limitation	5 (14%)
More than 1.0 km	7 (19%)
500 m to 1.0 km	12 (32%)
Less than 500 m	8 (22%)
Tied to the house	4 (11%)
Unable to walk	2 (5%)

4 Discussion

4.1 Interpretation of results

4.1.1 Basic characteristics

Arthroplasties are a therapy for disease patterns of mostly elderly patients, which is reflected in the demographic values in the present study with a mean age of 74 years and the youngest patient treated being 45 years old. A similar distribution is found in various other studies on this topic [58,59,123,124]. The gender distribution in the analysed cohort was balanced.

The average follow-up period of 25 months seems adequate. The main goal of this study was to analyse the results of the performed therapy in terms of eradication of infections. Therefore, the infections occurring within the first dozen months after finished treatment of infection are of major interest, as they are seen mostly as a consequence of the surgical intervention, for example by Zimmerli et al. [21]. This is also visible in the present Kaplan-Meier curve: most of the recorded treatment failures occurred within the first two years.

4.1.2 Type of infection

Because of the differing classifications of periprosthetic joint infections and varying study design, comparison of distribution of the presumed pathogenesis of infections seems not always appropriate. While the respective periods of time are varying throughout the studies, the principle classification by time into acute and chronic infections, in some cases with delayed infections as intermediate stage, is maintained. The distribution of the presumed route of infection in the present study corresponds with two thirds chronic infections and one third acute infections roughly to other conducted studies [51,125,126]. Also in earlier studies, a similar distribution was reported. Tsukayama et al. conducted 1996 a study on 97 patients with 106 infected hips. When interpreting the two subgroups “late chronic infection” and “positive intraoperative cultures”, describing patients with no clinical signs of infection, as chronic infections, 62% of infections were chronic [51]. Recently, in a study on 30 streptococci-associated periprosthetic joint infections Akgün et al. found 2017 47% of infections defined as late [124]. This lower rate of late or chronic infections may be due to the causing pathogen.

As already stated in the introduction, the most crucial question is, where to set the threshold between acute and chronic infections; more specifically, when an immature biofilm grows mature, remains still unclear. This situation is unsatisfactory, as the decision to retain a prosthesis and the choice of regimen of therapy depend on this fact. Recent classifications tend to a more cautious period of 4 weeks [63].

In the present study this classification would have resulted in a lower number of acute infections, but would not have changed the outcome significantly. This due to the fact, that anyway most of patient were treated by a two-staged exchange, as discussed in the following subchapter.

The type of infection was found to be a significant factor of outcome as acute postoperative infections showed an inferior outcome compared to acute hematogenous and chronic infections. As the group of acute postoperative infections was small (12 patients), a valid multivariate statistical analysis was not applicable. As stated in the introduction, a thorough debridement alongside with an exchange of mobile parts is recommended in acute postoperative infections. A possible explanation is the lack of use of biofilm-active antibiotics, which is discussed in chapter 4.1.9. Another possible argumentation could be, that the extent of necessary debridement is underestimated in acute postoperative infections, as the deterioration of periarticular tissue is by the short development time in some cases not as advanced as in chronic infections.

4.1.3 Performed therapy and necessity of further surgical treatment

In the present study, in most of the cases a two-staged long-term exchange has been performed. Only few cases were treated by one-stage exchange or exchange of mobile parts, therefore a reasonable comparison to these regimen is not applicable because of the small numbers. This skewed distribution is caused in the low proportion of early postoperative infections and that treatment protocols were performed at the discretion of the treating physicians and their more conservative attitude, tending rather to a two-staged exchange than to a one-stage protocol. Therefore, usually early hematogenous and some early postoperative infections were treated also by a two-staged regimen.

The proportion of chosen therapy regimen in literature is various, usually a higher rate of performed one-stage protocols is found. In the already described study on a cohort of 30

periprosthetic streptococcal infection, Akgün et al. reported a two-stage exchange in 73% of cases [124]. Choi et al. reported in a study comparing a one-staged and a two-staged exchange protocol in 44 out of 83 cases a two-stage exchange and in 22 cases an explantation without reimplantation [126], what may be accounted as aborted two-stage protocol. This would result in overall rate of two-stage exchanges of 79%. On the other hand, Tsukayama et al. performed 1996 in the majority of cases a one-stage protocol with either retainment of the implants or complete exchange of the prosthesis in 69 of 106 infected hips, which equals 69% [51]. It should be noted that 31 of these cases were diagnosed retrospectively as periprosthetic joint infection by microbial analysis of the intraoperative obtained tissue samples, which may explain a rather high share of one-stage exchanges in a time, when commonly two-staged protocols where performed more frequently [51].

4.1.4 Rate of infection control

Two-staged exchange protocols are usually referred to as “gold standard” in terms of infection control, for example by Senthi et al. 2010 [111]. Though, they are associated with increased side effects compared to one-stage protocols, as for example Berend et al. showed 2013 in a study on 202 patients [123]. Clinical experience shows, that the interval phase after explantation with no joint replacement in situ, is experienced especially debilitating by the patients.

Disch et al. conducted a study of a two-stage exchange protocol without temporary spacer, including 32 patients with an average duration of the Girdlestone-situation of 13.1 months, ranging from 3 to 43 months. Out of 32 patients, 20 suffered temporary or permanent occupational disability after finished treatment. In 14 cases, a surgical revision was necessary after primary explantation, of which 9 were deep revisions of bone and soft tissue adjacent to the joint [127]. While this rate of disability may be caused in the rather long interval and in the relatively high rate of necessary revisions after primary explantation, this still demonstrates the increased side effects, long duration of therapy and costs of a two-staged protocol. Therefore, a one-staged protocol seems preferable.

In the present study, the overall treatment result in terms of infection control with a rate of 79% lies in the range of the results of other conducted studies, although for example Achermann et al. found a two-year survival rate of 92% in early infections treated by

partially one-stage and partially two-stage protocols [59], which may be due to the presumed pathogenesis. Disch et al. found rate of infection control after implantation of 93.4% [127]. This good rate of treatment success may be caused in the already mentioned rather long interval between implant removal and reimplantation. The presumed route of infection was not clarified. Berend et al. found in 202 patients treated by two-stage exchange an overall rate of infection control of 76% with a minimum follow-up of 24 months [123]. Kubista et al. reported in 368 patients with infected knee arthroplasties treated by a two-stage revision protocol a recurrence of infection in 15.8% of cases [128], equalling 84.2% of cases with an infection control.

Concerning one-stage exchange protocols, good results using antibiotic-impregnated bone graft were found by Winkler et al. 2008, with 92% of infection control [58], though not clarifying the distribution of the presumed pathogenesis. In a Dutch retrospective analysis of 60 patients with *Cutibacterium* (formerly known as *Propionibacterium*)-associated infection of hip-, knee- and shoulder arthroplasties using mostly a one-staged exchange protocol, Meermans et al. found 93% of one-year and 86% of two-year infection free rate, respectively [129]. Tsukayama found in the above described study on 106 hips a rate of 80% of infection control after first treatment of mostly one-stage exchange protocols [51]. As 31 of these cases were preoperatively diagnosed as aseptic loosening and defined retrospectively by a positive intraoperative tissue culture as infected, a complete exchange of loose implants was performed and after diagnosis of infection antibiotics were administered for 6 weeks postoperatively. This may rise the rate of false-positive microbial findings, which will naturally have a lower risk of persistence of infection.

Likewise, meta-analyses found values within the range of the listed studies. Wu et al. found 2014 in a systematic review of the available literature an average rate of infection control of two-stage exchange protocols of 79.1% with a range from 33.3% to 100% [130]. In another review conducted 2012 by Lange et al. focused on chronic infections including 36 studies, an overall reinfection rate of 13.1% after one-stage compared to 10.4% after two-stage exchange was found [131], equalling a rate of infection control of 86.9% and 88.6% respectively. Kunutsor et al. reviewed 38 one-stage and 60 two-stage studies and stated a two year reinfection rate of 8.2% in one-stage and 7.9% in two-stage studies, respectively [132].

In the first instance, these numbers show, how tough in some cases eradication of periprosthetic joint infections is even by a two-staged exchange, but on the other hand, that in certain study populations, good results seem possible to achieve. Concerning the latter point, Jackson and Schmalzried reported 2000 in a review, that four common factors were associated to the success of one-stage exchange protocols: “(1) absence of wound complications after initial hip replacement; (2) good general health of the patient; (3) methicillin-sensitive *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Streptococcus* species and (4) an organism that was sensitive to the antibiotic mixed into the bone cement” [133].
In the second instance, it is to question, if there are individual factors which lead to a decreased rate of infection control of the present study in comparison to these studies with a reported more favourable rate.

4.1.5 Microbial findings

The microbial spectrum found corresponds in essence to other conducted studies [51,56,125,134], with coagulase-negative staphylococci (38%) and *Staphylococcus aureus* (15%) being most frequently found. Kliushin et al. analysed 2017 the pre- and intraoperative findings of 73 patients with chronic periprosthetic joint infections. As preoperative samples, they used discharge from wounds or sinuses, which were frequently reported in their cohort with present sinus tracts in 89% of all cases and present wounds in 8%. In case of absence of a sinus tract or wound, they performed an aspiration of the affected joint. As intraoperative samples tissue from the approach to the joint was used, usually five to six samples were collected. While focusing on chronic periprosthetic joint infections, they found a higher share of staphylococci being identified in 60% of cases [135]. Concerning this value, two issues could be an explanation. First, that using material from sinus tracts and open wounds will likely yield results containing the residual skin flora with inter alia a high share of staphylococci. At least, Mackowiak et al. reported on this issue 1978 comparing the results of sinus-tract cultures to cultures of intraoperative samples in patients with chronic osteomyelitis. In the sinus-tract cultures in 65% of cases staphylococci were found, while only 44% of sinus tract cultures contained the pathogen found afterwards in the culture of intraoperative samples [136]. Therefore, the use of this material is not recommended [46]. Secondly, the high rate of present sinus tracts could be associated with a higher share of staphylococcal infections.

Holleyman et al. reported 2016 also an increased rate of staphylococcal infections by reviewing two national databases containing information regarding arthroplasties and microbial findings and linking them. After identifying 75 primary knee arthroplasties which were treated by surgery because of infection, they found in 51 cases (equalling 70%) staphylococci as single causing pathogen. Main drawback of this study is, that any pathogen isolated up to 180 days before revision surgery were interpreted to “likely to represent pre-operative joint cultures” [137]. Therefore, it seems possible, that samples not associated to the following periprosthetic joint infection are included in the study. Tsukayama et al. reported an even higher share, with 81% of staphylococci associated infections [51].

The present proportion of methicillin-resistant staphylococci of 7% of all infections caused by *Staphylococcus aureus* or 2.4% of overall identified pathogens is lower than in other studies. Holleyman et al. reported in the above mentioned study a share of methicillin-resistant *Staphylococcus aureus* or *epidermidis* of 33% out of the group of infections by *Staphylococcus aureus* and 17%, respectively, of overall found pathogens [135]. Achermann et al. found 24 out of 26 findings of coagulase-negative staphylococci to be methicillin-resistant [59].

4.1.6 Discordant microbial findings

The microbial results of the aspirations and of the biopsies performed prior to the first septic surgery have been compared to the results of microbial analysis of tissue samples collected during the first surgery. Aspirations have shown concordant positive or negative results in 68% cases, while concerning biopsies this value decreases to 61%. Especially considering, that within the group of concordant positive results discordant positive microbial are included, these values seem not satisfactory.

Other recently conducted studies showed similar results. Kliushin et al. compared in the above-mentioned study 2017 the results of microbial analysis of pre- and intraoperative samples and reported a complete correspondence in 50.7% of [135]. Again of note, that the use of material collected from sinus tracts and wounds was reported to have a high rate of false-positive results of the skin-flora [136].

Holleyman et al. conducted 2016 another study resembling to the above-mentioned study reviewing the causing pathogens of 248 hips [138]. Similar to the first study, they used data of a national database containing data concerning primary and revision knee-arthroplasties and linked it to a second database containing data of microbial analyses, identifying 75 cases with preoperative microbial findings available. Out of 75 cases, the preoperative identified pathogens were similar in 75% of cases and antimicrobial sensitivities matched in 49% of overall cases and in 66% of cases with matching pathogens, respectively [137]. Drawback of Holleyman's study is, that preoperative samples were collected partially up to 180 days before the surgery and therefore a shift of pathogens seems possible.

The problem of discordant microbial results of pre- and intraoperative samples was reported already in earlier publications. Buchholz et al. compared 1981 organisms identified by a preoperative aspiration and by intraoperatively collected tissue samples of 205 infected hip arthroplasties. In 73% the same organism was identified, in the rest of cases the results were contradictory [139].

4.1.7 Sensitivity and specificity of aspiration and biopsy

In the conducted study, the sensitivity of the aspiration was found to be at 84.6% and the sensitivity of the biopsy at 78.5% taking only microbial analysis into account. When using a combination of histopathologic and microbial methods this value increases to 85%, which underlines the clinical importance of both microbial and histopathologic examination of collected samples. These values correspond to the values reported in other studies, although Gollwitzer et al. reported 2006 in a review various sensitivities ranging from 12% to 100% [140].

Concerning preoperative biopsies in case of chronic periprosthetic joint infections, Bauer stated already 2006, that the biopsy is a "tarnished gold standard" [60] inter alia because of false positive or discordant positive findings compared to results of microbial analysis of intraoperative collected tissue samples.

Possible explanations for disparate findings in studies are the specific microbial culture conditions, type of the analysed sample (smear, aspirated fluid or tissue) and possible prior intake of antibiotics. An additional difficulty for detection is, that bacteria present in

their sessile form are situated within a biofilm, which is why there is only a limited exchange to the synovial fluid [141]. Another explanation is, that the prolonged doubling-time of sessile bacteria must be considered regarding the time of incubation. In 110 patients, a detection rate of 73.6% percent have been found for a seven day incubation period in comparison to a 14-day period [142].

A possible explanation for a decreased rate of infection control could be, that in the present analysed cohort usually less than the recommended five to six tissue samples [74] have been collected throughout the therapy and thereby the causing pathogens were not properly identified. This could be an argument especially concerning treatment failure of cases with unidentified pathogen, but in this group the rate of treatment failure was at 12% comparatively low. Still, this would not explain discordant results of pre- and intraoperative microbial findings, since a smaller number of tissue sample is not likely to increase the rate of false-positive or disparate findings. Additionally, Peel et al. concluded recently, that 4 tissue samples are sufficient. They compared inoculation of samples into blood-culture bottles and conventional culture techniques and used Bayesian latent class modelling to estimate the respective optimal number of samples [143].

Discordant microbial results can either be caused in errors of preoperative or intraoperative collected materials. In the mentioned studies, the intraoperative collected samples are used as reference for pre-operative diagnostics [73,135,143,144].

Improvements for pre-operative diagnosis of especially chronic infects are needed. One alternative has been conducted 2011 by Corona et al. in form of the percutaneous interface biopsy. With a trocar cylinders of the implant-bone or cement-bone interface are collected percutaneously. In a cohort of 24 patients, the found sensitivity was 88.2% combined with a specificity of 100% [145]. Concerning both pre- and intraoperative collected tissue samples, another option is optimization of cultural methods. Peel et al. found in a series of 369 patients, that using blood culture bottles for tissue specimen increased sensitivity for diagnosis of periprosthetic joint infection by 47% (from 62.6% to 92.1%) compared to the use of conventional agar and broth cultures [146].

Concerning detection of the causing pathogens by material collected during the operation, the sonication seems especially regarding biofilm-associated diseases of solid

indwelling devices as chronic periprosthetic joint infections a promising method. Several studies found an increased detection rate of sonication compared to conventional cultural methods. As stated in 1.2.3, Trampuz et al. analysed 2007 the results of sonication and conventional cultural methods of 79 infected arthroplasties out of 331 removed knee or hip arthroplasties and found a sensitivity of conventional cultural methods compared to sonication of 60.8% to 78.5%, respectively, while the specificity was 99.2% to 98.8%, respectively. Out of 79 patients, in 14 cases pathogens were identified by sonication while tissue culture yielded negative results. In 11 cases contradictory, positive results were found. Especially in case of prior intake of antibiotics 4 to 14 days before collection of samples, the advantage of sonication was increased [84].

Portillo et al. analysed 2014 in a similar study overall 231 removed implants, of which 69 were classified as infected. They conclude, that major advantages of sonication are an increased number of detected pathogens and the results are available earlier compared to conventional cultural methods. In 69 cases of infected arthroplasties the sonication detected pathogens in 56 patients compared to 42 patients by conventional cultural methods. The results were available concerning sonication in 26% and 48% on day one and two, respectively, compared to 13% and 28% of conventional tissue culture [82]. Though, their analysis does not take account of the microbial concordance of results of the two groups, but only reported positive and negative findings. Furthermore, they found contradictory results to the previous mentioned study concerning prior antibiotic intake. While Trampuz et al. found an advantage of sonication especially 4 to 14 days after prior antibiotic intake Portillo et al. [84] conclude, that tissue samples are less affected by it, as they found in the group with no prior antibiotic intake (36 patients) 20 cases (55%) of positive tissue cultures and 31 (86%) of positive sonication results, while this value were in the group with prior antibiotic intake (33 patients) 22 (66%) and 25 (75%), respectively [82].

Major drawback of sonication is a matter of principle: since implants are needed, it cannot be used as a pre-operative test. Given the unsatisfactory situation of a considerable treatment failure rate in terms of infection control and frequent discordant microbial results, these numbers show the possible impact of sonication to the treatment of periprosthetic joint infections. Of note, that also by using sonication, both above-mentioned studies reported 19% [82] and 21% [84], respectively, of culture-negative cases.

The affection of tests by prior antibiotic intake is an important issue, since in two-staged protocols – as also in the present study – frequently a biopsy is performed before reimplantation to prove the eradication of pathogens. To diminish this affection, commonly 14 days between prior antibiotic intake and collection of samples are recommended [56,147]. Results of conducted studies show, that the time-span of 14 days is possibly chosen to short.

Barrack et al. analysed 1997 a series of 69 knee arthroplasties in 67 patients, who underwent aspiration of the knee and in which 20 turned out to be infected. No patient took antibiotics within 14 days before the aspiration, but 16 in the time before. The sensitivity of aspiration in the group with prior intake of antibiotics was significantly decreased at 42% compared to 75% in the group with no prior antibiotics [68]. The optimal time of antibiotic-free period before culture sampling seems unknown.

4.1.8 Use of a temporary spacer

One possible factor affecting the rate of infection control in the present study, is the rather large proportion of hips treated without the use of a temporary spacer. This group of patients with infected hip arthroplasties, treated by a two-stage exchange without a spacer, showed a higher rate of necessary re-debridements after initial explantation as well as recurrence of infection after performed reimplantation.

Current studies cannot clearly answer the question, if antibiotic-loaded spacers in infected joint arthroplasties are necessary or not. In an already mentioned study conducted by Disch et al. 2007 on 32 infected hip arthroplasties treated with two-stage revision hip surgery without the use of a temporary spacer, good results have been demonstrated, with a rate of reinfection rate after reimplantation of 6.3%. Though, in 14 of 32 patients (equalling 44%) revisions had to be performed after explantation, of which 9 were re-debridement of bone or soft-tissue because of persisting deep-infection [127]. On the other hand, a prospective study on infected hip arthroplasties comparing a group of 30 patients treated with two-stage revision without spacer to 38 patients treated with a vancomycin-loaded spacer found a significantly better outcome regarding infection control (66.7% vs. 89.1%) and clinical results in follow-up (60.0 % vs. 81.5%) in the group treated with spacer [134]. Berend found a rate of infection control of 76% when performing

a two-stage exchange regimen with a spacer used [123].
As stated in the introduction in chapter 1.2.3, arguments for the use of a spacer are the possibility of local drug elution in high dosages, a diminished dead-space after explantation and prevention of shortening of the joint and surrounding soft tissue. A drawback in the use of temporary spacers is the possible colonization of bone cement, although Griffin et al. found 2012 by the means of electron microscopy scanning and confocal scanning microscopy in small series of six patients treated with vancomycin/tobramycin loaded spacers no present bacteria or biofilm on the surface of explanted spacers. Contrary to that, Belt et al. found by analysis of removed bone cement by extensive culture procedures present bacteria in 18 of 20 cases [148] and Mariconda et al. found by examining a series of 21 explanted spacers by sonication in 6 cases positive findings [149].

4.1.9 Biofilm-active therapy

Another cause for an increased rate of treatment failures could be, that biofilm-active antibiotics after reimplantation were used only in the minority of cases, although there was no statistical significant difference found. The results in the group of acute postoperative infections point to a higher importance of biofilm-active therapy in one-stage protocols.

Concerning the clinical efficacy of biofilm-active antibiotics, studies are lacking, while the in vitro efficacy of biofilm-active antibiotics is well established [45]. Köder found 2017 in a cohort of 93 spinal implant-associated infections 84% of two-year survival rate in the group treated with biofilm-active antibiotics compared to 49% without (unpublished data, personal communication). Contradictory to that and the in-vitro findings, Jacobs found in a series of 60 patients with infected shoulder, hip and knee arthroplasties no significant difference depending on the use of rifampicin in outcome after one and two years. Of note, that the majority of cases was treated by one-stage exchange (47 of 60 patients) and that out of 39 cases treated with rifampicin, in 33 cases it was used in combination with clindamycin [129]. As they also stated, several authors found a reduced plasma concentration of clindamycin when given in combination with rifampicin. For example, in a retrospective analysis of 70 patients treated with a continuous clindamycin infusion, a significantly lower median serum concentration of clindamycin was found, when patients were treated additionally with rifampicin [150].

On the other hand, Tsukayama et al. reported already 1996 good results, presumably without special attention to biofilm-active antibiotics, as they at least did not specify the performed systemic antibiotic therapy [51]. Nevertheless, as already a certain time passed after this study, a general shift in microbial resistance is possible.

4.1.10 Functional outcome

The outcome regarding pain is satisfactory, given that most of respondents take only little or no analgesics. The functional outcome regarding the ability to walk as well as the ability to ascend or descend stairs is not satisfying, since roughly half of respondents are able to walk more than 500 metres and around 40% of them must use walkers or other axillary crutches, what means, that they can be referred to be impaired. Also, the WOMAC-Score results regarding functional outcome with an average score of 2.1 out of 4 per question show, that the patients are limited in their everyday lives. These answers demonstrate, how devastating the side-effects of the therapy are. As mentioned above, Disch et al. reported similar results regarding the functional outcome [127].

4.2 Methodological critique

Limits of this study are caused in the observational, retrospective design. As only a little number of one-stage exchanges was performed, no valid comparison of one-stage and two-stage exchange was possible. Concerning the analysis of functional outcome, main drawback is the mediocre feedback-rate (52 of 104 patients) and participation-rate (38 of 104 patients), respectively.

The mean follow-up period was 25.1 months, what seems sufficient. However, it is possible, that some treatment failure can occur in the following years. New outcome studies require follow-up periods up to 5 years. This data is not yet available for our study patients. In future, cohort studies with an increased follow-up time of 10 or 20 years may provide more inside information on ling-term follow-up regarding infection and functional outcome.

4.3 Conclusion

There are important questions, that cannot be answered by this study design. First and foremost, the randomly prospective comparison of one-stage and two-stage exchange protocols is still lacking. The impact of biofilm-active antibiotics has to be proven in bigger studies. The present results could be interpreted, that in one-stage protocols the biofilm-active therapy is more important than in two-stage long-term protocols. The restriction must be made, that especially one-stage exchanges were performed in the present study only in the minority of the cases.

Another important issue to solve is, to provide a valid classification regarding the time spans between implantation, onset of symptoms and start of therapy including the respective diagnostic decisions.

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II - Figures

III - Tables

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Affidavit

I, Jan Schwetlick certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Analysis of the epidemiology and therapy of periprosthetic joint infections of total hip- and knee arthroplasty. A retro- and prospective study on „Klinikum im Friedrichshain, Berlin“ 2010 – 2015“. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The section on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) corresponds to the URM (see above) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.
The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

23.12.2018 _____
Signature

Signature, date and stamp of the supervising University teacher

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Signature of the doctoral candidate

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