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Habilitationsschrift

Analysis of risk factors leading to failure in septic two-stage exchange arthroplasty

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Abbreviations

DTT	Difficult-to-treat
DNase	Deoxyribonuclease
EBJIS	European Bone and Joint infection Society
IDSA	Infectious Diseases Society of America
MiRNA	MicroRNA
MSIS	Musculoskeletal Infection Society
PJI	Periprosthetic joint infection
THA	Total hip arthroplasty
TKA	Total knee arthroplasty

1. Introduction

1.1. Significance of periprosthetic joint infection as revision cause

Arthroplasty of the hip and knee joint is a successful elective surgical procedure with more than 95% survivorship at 10-year follow-up in patients with advanced osteoarthritis [4, 5]. In the last decades there was a major increase of the number of implanted arthroplasties in Germany and about around 300.000 hip and knee arthroplasties were performed in the year of 2014 [6]. Similar to the trend in Germany in the UK and USA more than 800.000 arthroplasty surgeries are done annually [7], with expectations that more than 4 million arthroplasty surgeries will be performed by the year 2030 [4]. Concomitantly, the number of revision surgeries is expected to be on rise. Periprosthetic joint infection (PJI) is estimated to occur in 1-2% in primary and in 4% in revision arthroplasties [3, 4, 8-10] and was in Germany the second frequent reason for revision surgery in patients with primary hip arthroplasty after aseptic loosening in year 2015 [3]. Revision procedures continue to impose substantial economic and social burdens, studies showing higher costs, longer hospitalization and higher number of readmissions in patients with revision surgery due to PJI than patients with a primary arthroplasty [1, 11] (Figure 1).

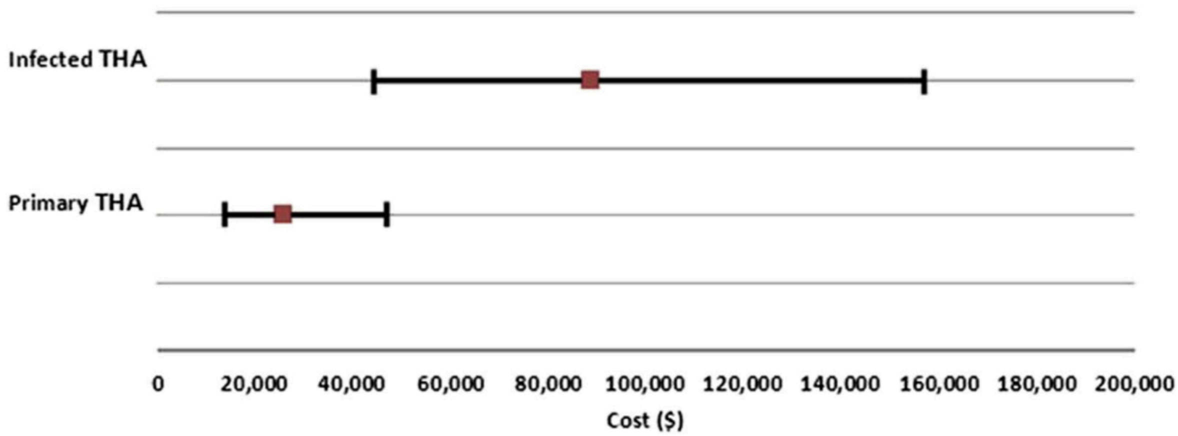

Figure 1: Costs for the infected total hip arthroplasty (THA) and matched noninfected THA [1]. Reprinted with permission from Elsevier.

Infection costs in the USA alone was expected to be more than 900 million US dollars in 2012 with projections to be greater than 1.6 billion US dollars by 2020 [2, 12] (Figure 2). Moreover, PJI has a major effect on functional outcome and mortality of the patients, as the relative mortality risk of a patient, who undergoes a revision due to PJI is 2.18 times higher compared to a patient, who do not require any revision surgery after primary arthroplasty [13]. One-year mortality could even be 3.1 times higher in patients with enterococcal PJI than is the case with all other types of bacteria [13].

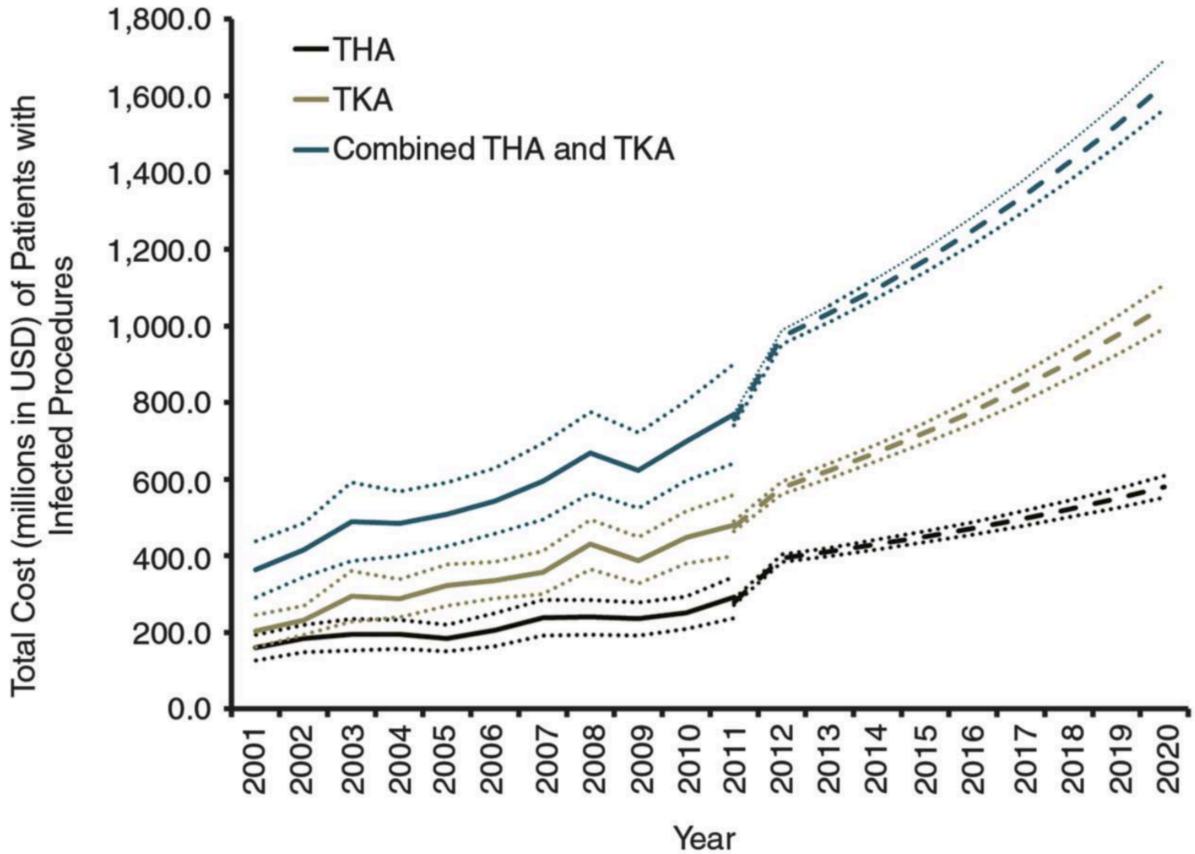

Figure 2. Estimated historical (2001-2011) and projected total inpatients cost of infections with total hip arthroplasty (THA), total knee arthroplasty (TKA) and combined THA and TKA procedures within the United States between 2001 and 2020. Solid lines represent the historical trends; dashed lines are projected values for each procedure. For both historical and projected values, the dotted lines represent the 95% confidence intervals [2]. Reprinted with permission from Wolters Kluwer Health, Inc.

1.2. Pathogenesis of PJI

Classification of PJI depends on the type of pathogenesis and the time of symptom manifestation after prosthesis implantation [14]. Pathogenetically, seeding of the microorganisms can be either exogenously or hematogenously [15]. Around two thirds of

PJI occur typically exogenously due to intraoperative inoculation of the implants or in the early postoperative phase in case of wound healing complications [9]. Hematogenous infections are caused by a seeding from a distant primary focus via blood stream at any time after surgery [16]. Therefore, all implants remain susceptible to hematogenous infection during their whole indwelling time, as high vascularity of periprosthetic tissue and presence of a foreign body weakens the host defense [3].

Timely manifestation of PJI depends mostly on the virulence of the causative microorganism. Early infections (< 2 months after surgery) are associated with clear clinical signs of infection, such as redness, swelling, fever and frequently caused by high-virulent microorganisms such as Staphylococcus aureus or streptococci, while patients with delayed infections (between 2 months and 2 years after surgery) present often with a stealth-type of infection, having mostly chronic pain as the only symptom [9]. The latter is typically caused by low-virulent microorganisms, such as coagulase-negative staphylococci or Cutibacterium acnes [17]. Late infections (> 2 years after surgery) are typically caused by hematogenous seeding of high-virulent microorganisms, leading therefore mostly to acute onset of symptoms. Skin and soft-tissue infections and cardiovascular infections are the most common origins of hematogenous spread [16]. Other less frequent origins include urinary, respiratory or gastrointestinal tract, as well as oral cavity [18]. Although the identification of primary infectious focus in hematogenous PJI is crucial to prevent recurrences, the primary focus can be found out only in 68% of the cases [16].

1.3. Role of biofilm

Microorganisms persist preferentially in biofilms, rather than in free-floating planktonic form in most environments, including human body [19, 20]. Within biofilms, microorganisms are surrounded of a polymeric matrix and create well-organized complex communities, mimicking multicellular organisms [9, 21]. An estimated 80% of human infections and most of the PJIs are attributed to biofilms, where the microorganisms escape from host defense and are up to 1000 times more resistant to antimicrobial agents than their planktonic counterparts [3, 22, 23]. Moreover, the surfaces of commonly implanted foreign bodies such as titanium, stainless steel, cobalt-chromium and polymethylmethacrylate are highly susceptible to infection and reduce the minimal infecting dose of microorganisms more than 100,000-fold [24-26]. Therefore, antimicrobial activity requires penetration into the biofilm matrix to eradicate infection. High biofilm activity could have been demonstrated in recent studies only for few antibiotics, including rifampicin against staphylococcus infections and ciprofloxacin against Gram-negative infections [27-30]. Better cure rates were achieved in patients with PJI, if biofilm-active treatment was used, compared to conventional regimes [31-35]. Therefore, it is believed that microorganisms, for which no biofilm-active antimicrobial therapy exists, associate with worse treatment outcomes and are referred as difficult-to-treat (DTT) [14, 36]. Given that most of the current antibiotics tend to suppress rather than eradicate biofilms, there is an urgent need for biofilm treatment in patients with PJI [20].

1.4. Management of periprosthetic joint infection

The main purpose of PJI treatment is to achieve a pain-free and functional prosthetic joint, which can be best achieved by a combination of antimicrobial and surgical therapy. The initial antimicrobial therapy is mostly empiric and often applied intravenously to lower the bacterial load prior oral treatment [14]. After identification of the causative microorganisms a targeted therapy should be applied according to the recommendation of the infectious disease specialists depending on the antibiotic susceptibility. A therapy with rifampin or fluoroquinolones should start only after reimplantation (in case of an exchange arthroplasty), when all drains are removed and the wound is dry, not to emerge any antibiotic resistance [37]. Currently there are no controlled studies testing the ideal length of the antimicrobial treatment, however a total antimicrobial treatment of 12 weeks is mostly recommended in literature [3, 38]. Surgical techniques include debridement with retention of the prosthesis, one- or two-stage exchange, resection arthroplasty, arthrodesis and amputation depending on the infection duration and severity [9]. Figure 3 summarizes most important treatment options and antimicrobial treatment strategy. Debridement and implant retention can be performed successfully in acute infections when: (1) prosthesis is stable; (2) duration of symptoms is short; (3) soft tissues are intact; and (4) difficult-to-treat microorganisms are absent [15, 39]. In cases with longer duration of symptoms with maturation of the biofilm a complete removal of the arthroplasty is mandatory. One-stage exchange is gaining popularity as data continue to show similar outcomes compared to a two-stage exchange [40, 41]. The most important profit of this procedure is that explantation and reimplantation is performed in a single surgery and hospitalization. Despite indications and contraindications for one-stage exchange are changing with time, overall strict exclusion criteria include culture-negative infections, severely compromised bone and soft tissues, antibiotic-resistant microorganisms, enterococcal infections, and history of a prior surgery due to infection [41-44].

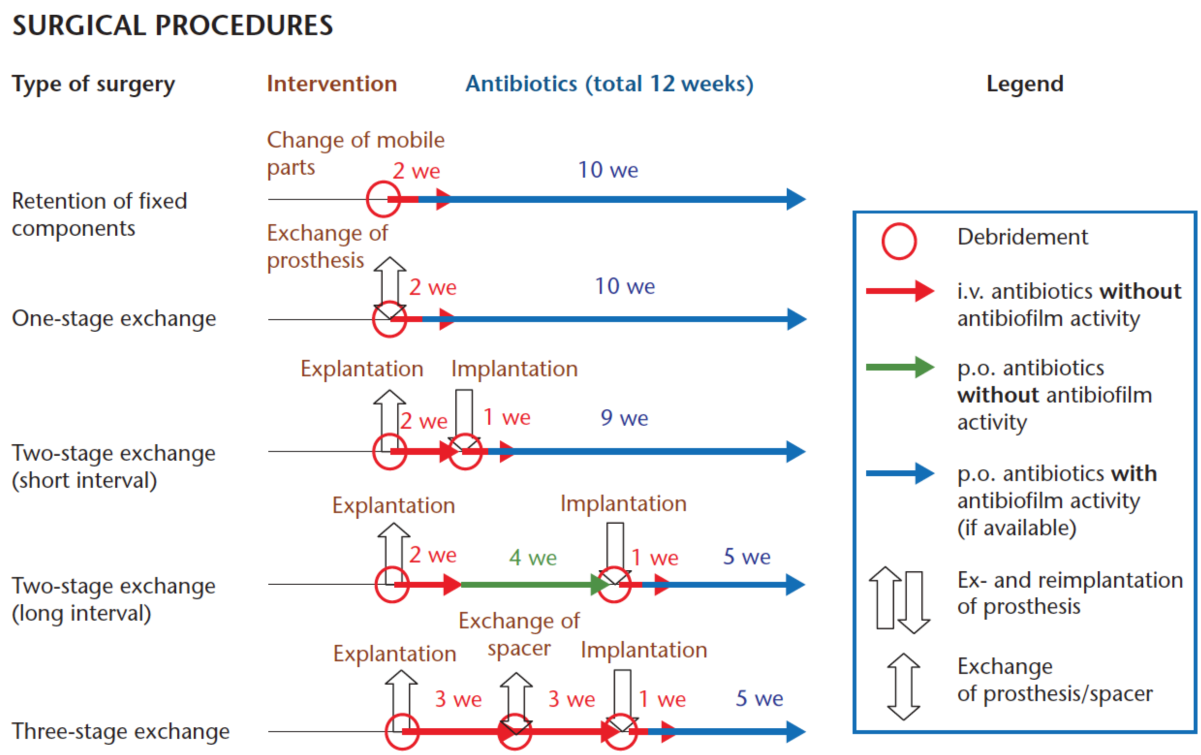

Figure 3. Overview of surgical procedures and antimicrobial therapy strategy [3]

Although the best treatment option of PJI is unclear, two-stage exchange arthroplasty, including removal of the components and insertion of an antibiotic-impregnated cement spacer in the first stage and reimplantation of the prosthesis at a later stage, still remains the gold standard for the treatment of chronic PJI in most countries [45]. The first stage consists of removal of all the implants, as well as all infected and necrotic tissue, bone cement and all other foreign material, which can maintain infection. An antimicrobial-impregnated spacer can then be placed to keep the limb at its correct length. Recently, a study showed significantly greater range of motion and higher Knee Society scores, as well as shorter hospital stays in patients with articulating spacers compared to patients with static spacers for the treatment of knee PJI [46]. The second stage is mostly used as another opportunity to perform a substantial debridement before the reimplantation of the definitive prosthesis.

1.5. Outcomes after two-stage exchange arthroplasty

The management of PJI continues to be challenging and incurs higher complication rates and poorer patient outcomes compared with primary total joint arthroplasty [47]. A reinfection after a failed PJI treatment could ultimately result in further high economic costs and worsen patient outcomes. Factors affecting the successful eradication of PJI include host comorbidities, soft tissue conditions, virulence of the affecting microorganism, antimicrobial treatment and the surgical technique [47-50]. The reported outcomes in literature after two-stage exchange varies, with some studies showing a 100% rate for infection eradication [47, 51-58]. However, the results remain unpredictable, as current data regarding PJI may lead to unfounded, inaccurate conclusions and some rates of failure of > 20% continue to be reported [50, 54, 59, 60]. Moreover, the absolute number of patients with treatment failure can be more than reported. The majority of those studies focused on the clinical outcome following reimplantation does not accurately reflect the overall success rate of two-stage exchange, since patients, who do not undergo reimplantation after the first stage are not included in the calculations. Recent studies were able to show, that 1 in 5 patients undergoing the first stage do not undergo subsequent reimplantation for a variety of reasons, such as infection persistence or mortality [51, 55, 61]. Independent significant risk factors for mortality are host grade and severe comorbidities, which are also associated with failure after two-stage exchange arthroplasty [51, 61]. Furthermore, patients with persistent infection after the first stage, who undergo a spacer exchange demonstrate poorer outcomes, including failure to undergo reimplantation and twice the failure rate [45]. Current two-stage exchange protocols remain imperfect to address PJI. With the knowledge of PJI pathogenesis and risk factors for failure, optimization of current treatment strategies is needed to improve outcome of patients with PJI [54].

1.6. Scientific question

There is a great need to identify the factors leading to failure to ultimately achieve a successful two-stage exchange and to optimize infection-free survival. The purpose of this habilitation script was scientific evaluation of factors predictive of failure in a two-stage arthroplasty in patients with knee and hip PJI and to find answers to the following questions.

- Can PJI patients infected with microorganisms, for which no biofilm-active treatment exists, be treated as successfully as PJI patients with more susceptible microorganisms with a two-stage exchange arthroplasty?
- What is the association between positive cultures at the time of reimplantation and subsequent failure in two-stage exchange arthroplasty?
- What is the role of patient independent risk factors, such as selection of surgery strategy, type of antimicrobial treatment and missed infection foci, in the failure of two-stage exchange arthroplasty?
- Can a multidisciplinary team approach provide better outcomes in the treatment of patients with PJI?
- Are all reinfections after a presumed successful two-stage exchange arthroplasty persistent infections and should be treated with a new two-stage exchange

2. Results

2.1. Streptococcal periprosthetic joint infection

High failure rates in treatment of streptococcal periprosthetic joint infection

Akgün D, Trampuz A, Perka C, Renz N. Bone

Joint J, 2017;99-B:654-9

https://doi.org/10.1302/0301-620X.99B5.BJJ-2016-0851.R1

Introduction

Invasive streptococcal infections in adults are in increase in last two decades, involving also periprosthetic joint infections, so about 10% of PJIs are caused by these microorganisms and the frequency is expected to rise [62, 63]. Although streptococcal infections were thought to be easy to treat due to their broad antimicrobial sensitivity, recent literature has shown conflicting data about the outcomes of treatment for streptococcal PJI [62, 64-66]. Furthermore, it is unknown, whether rifampicin, which plays a key role in eradication of staphylococcal biofilms, is also effective against biofilm built by streptococci [14]. The purpose of this study therefore was to evaluate the pathogenesis, clinical characteristics and outcomes of treatment in patients with streptococcal PJI. Furthermore, the influence of rifampin on the treatment outcome was also analyzed [49].

Methods

30 Patients with a streptococcal PJI (12 hip and 18 knee arthroplasties) treated between January 2009 and December 2015 were included in the study. The Kaplan-Meier survival analysis was performed to assess the probability of infection-free survival.

Results

The infection was hematogenous in 16 and perioperative in 14 patients. The infection-free survival at three years with 12 patients at risk was only 59% (95% confidence interval 39-75%) [49]. Furthermore, treatment failure was observed in 45% of the patients, who were managed with a two-stage exchange arthroplasty. Treatment with or without rifampin included in the antibiotic regime did not change the treatment outcome (p=0.175)

Discussion

This study showed a very low success rate in patients with streptococcal PJI in contrast to former belief, that streptococcal infections are easy to treat due to wide spectrum of antimicrobial sensitivity. The common route of infection is hematogenous and the most failures occur in the first year after treatment, so treating physicians should prompt a search for the potential primary source of infection, follow-up their patients closely and consider long-term antimicrobial suppression in order to optimize the treatment outcome [67]. The results of this study raise the question, whether streptococci should be classified as difficult-to-treat microorganism, which are associate with worse treatment outcome due to the lack of existing biofilm-active antimicrobial therapy [14].

2.2. High rate of infect eradication in patients with difficult-to-treat microorganisms

Outcome of hip and knee periprosthetic joint infections caused by pathogens resistant to biofilm-active antibiotics: results from a prospective cohort study

Akgün D, Trampuz A, Perka C, Renz N.

Arch Orthop Trauma Surg. 2018 May;138(5):635-642.

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Introduction

Implant-associated infection is caused by surface-adhering microorganisms persisting as biofilm, which is resistant to host defense and antimicrobial agents [14]. This topic is gaining more importance in the era of rising antimicrobial resistance and only few antimicrobial agents are available, which possess anti-biofilm activity such as rifampin against staphylococcal biofilms and ciprofloxacin against Gram-negative biofilms [27, 28, 68-70]. Recent literature showed higher rates of infection eradication in patients with staphylococcus PJI, who were treated with rifampin combinations compared to patients without biofilm-active agents [34, 35]. Therefore, it is believed that microorganisms, for which no biofilm-active antimicrobial therapy exists, associate with worse treatment outcomes and are referred as DTT [14, 36]. In patients with a DTT PJI a two-stage exchange with a long interval (>6 weeks) is recommended, however it is not known whether the absence of a biofilm active treatment adversely influences the treatment outcome compared to non-DTT PJI if a two-stage exchange is used [68]. The aim of this study was therefore to compare the outcome of patients with DTT and non-DTT PJI.

Methods

Patients with hip and knee PJI, who were treated in our institution between 2013 and 2015 were prospectively included in this study and Kaplan-Meier survival analysis was used to compare treatment outcome between patients with a DTT PJI and a non-DTT PJI.

Results

The treatment success rate was similar in patients with a DTT PJI compared to patients with a non-DTT PJI (80% vs 84%, p=0.61). Hospital stay, prosthesis-free interval and duration of antimicrobial treatment were significantly longer in patients with DTT PJI.

Discussion

Patients with a DTT PJI can be treated as successfully as patients with a non-DTT PJI, if longer prosthesis-free interval and longer antimicrobial treatment are carried out. However, some studies reported that some pathogens can be dormant for a long time in the absence of an implant and re-emerge at the time of reimplantation, which can lead to failure [5, 71].

2.3. Higher failure rate in patients with positive microbiology at the time of reimplantation

A positive bacterial culture during re-implantation is associated with a poor outcome in two-stage exchange arthroplasty for deep infection

Akgün D, Müller M, Perka C, Winkler T.

Bone Joint J. 2017 Nov;99-B (11):1490-1495.

https://doi.org/10.1302/0301-620X.99B11.BJJ-2017-0243-R1.

Introduction

The decision, whether to reimplant a new prosthesis or perform another spacer exchange at the time of the second stage in two-stage exchange arthroplasty is mainly based on intraoperative macroscopic appearance and combination of serological tests as well as aspiration analysis [72]. However, there are no well recognized tests or clinical analyses by which to determine the best time for the second stage [50]. Furthermore, the association between a positive culture at the time of the second stage and subsequent failure is unclear and only one study was able to find that a positive culture carries an increased risk of failure [59]. The purpose of this study was to analyze the relationship between a positive culture and the subsequent rate of failure in two-stage exchange arthroplasty.

Methods

A total of 163 patients with a hip or knee PJI between 2013 and 2015 were retrospectively included. Logistic regression analysis was performed to determine the predictors of risk factors for failure after two-stage exchange arthroplasty.

Results

The same initially infecting microorganism was isolated at the reimplantation in 33.3% of patients. The risk of failure of treatment was significantly higher in patients with a positive culture at the time of reimplantation (odds ratio=1.7, p=0.049) and in patients with a higher Charlson Comorbidity Index (odds ratio=1.5, p=0.001) [50].

Discussion

A positive culture at reimplantation and higher comorbidity were independently associated with two-times the risk of subsequent failure. Prolonged antimicrobial treatment after the reimplantation in patients with positive cultures should be implemented to enhance the infection eradication rate after two-stage exchange arthroplasty. Furthermore, medical optimization of patients with severe comorbidities plays a critical role in treatment success.

2.4. High rate of patient independent failure cause in treatment of periprosthetic joint infection

Failure analysis of infection persistence after septic revision surgery: a checklist algorithm for risk factors in knee and hip arthroplasty

Kilgus S, Karczewski D, Passkönig C, Winkler T, **Akgün D**, Perka C, Müller M.

Arch Orthop Trauma Surg. 2020 Apr 15.

https://doi.org/10.1007/s00402-020-03444-0

Introduction

Common risk factors affecting the successful eradication of PJI include host comorbidities, soft tissue conditions and virulence of the affecting microorganism [47-50]. However, in most cases the failure cannot be explained by these factors alone and treating physician dependent errors in surgical and antimicrobial treatment can play an essential role. This study aimed to identify those possible and specific reasons such as the selection of surgical strategy, type of antimicrobial treatment and missed infection foci

73.

Methods

The following text is adopted from the above mentioned publication [73]. In a prospective analysis all patients were included that were treated: (1) at our institution, (2) with a twostage exchange, (3) between 2013 and 2017, (4) due to an infection persistence after a previous revision for PJI. A checklist algorithm, which is based on international guidelines, was used to identify possible reasons for infection [73].

Results

In most of the patients (85%) included in this study at least one patient independent failure reason could have been identified. The leading error was inadequate therapy concept in 50% of the patients followed by inadequate surgical debridement (33%), inadequate antimicrobial therapy (30%) and missed external bacterial primary focus (13%). After the individual failure analysis, all 70 patients were treated with a two-stage exchange in our department and in 94.9% infection freedom could be achieved (34.3 ± 10.9 months follow-up) [73].

Discussion

In most of cases with treatment failure after septic treatment at least one possible treating physician dependent error can be found, of which inadequate antimicrobial treatment and inadequate debridement are the most important issues. Further diagnostic or therapeutic errors include the use of serum inflammatory biomarkers to rule out PJI, incomplete evaluation of joint aspirate and overreliance on suboptimal diagnostic criteria [74]. In patients with a treatment failure the entire previous management should be assessed for errors. A high rate of infection-free survival after two-stage exchange arthroplasty may be achieved by using a checklist algorithm and standardized treatment planned by a multidisciplinary team approach.

2.5. The importance of multidisciplinary team approach in the treatment of periprosthetic joint infection

High cure rate of periprosthetic hip joint infection with multidisciplinary team approach using standardized two-stage exchange

Akgün D, Müller M, Perka C, Winkler T.

J Orthop Surg Res. 2019 Mar 13;14(1):78.

https://doi.org/10.1186/s13018-019-1122-0.

Introduction

Multidisciplinary team approach plays an essential role in decision-making and have become the standard of care for malignant neoplasms in many countries. Especially in more complex cases it guarantees to define the best possible treatment plan specific for the patient [75, 76]. Recent literature also confirmed that multidisciplinary team approach may affect clinical outcome and patient survival [77, 78]. Similar to the treatment of patients with malignancy, management of patients with PJI involves multiple medical steps, which necessitates close interdisciplinary work-up of orthopedic surgeons, infectious disease specialist and microbiologist. The purpose of this study was to report the outcome of our two-stage revision protocol, in which a multidisciplinary team guides the management of all patients, and all diagnostic and treatment processes are based on a standardized algorithm [79].

Methods

The following text is adopted from the above mentioned publication [79]. All hip PJI episodes treated between march 2013 and may 2015 were prospectively included. The infection-free survival was assessed by using the Kaplan-Meier survival method. Furthermore, patients were dichotomized into two groups depending on the number of previous septic revisions, duration of prothesis-free interval, positive culture with difficult-to-treat microorganisms, microbiology at explantation and microbiology at reimplantation [79].

Results

A total of 84 patients could have been included in the study. The Kaplan-Meier estimated infection-free survival after 3 years was 89.3% with 30 patients at risk. Coagulase-negative staphylococci were the most common isolated pathogens followed by Staphylococcus aureus and Cutibacterium. There were no statistical differences in infection-free survival among the dichotomized groups.

Discussion

Management of prosthetic joint infections is a very challenging task with many possible sources of errors in the diagnosis and treatment. Thus, it obligates a multidisciplinary team approach in the management of the patients with PJI to achieve the highest infect eradication rates. Furthermore, it can lead to a decrease in the usage of antibiotics, a reduction in surgeries performed as well as shortened hospital stay, which not only reduces treatment side effects but also improves economic feasibility [75]. The members of the multidisciplinary team should also follow-up their patients after the treatment closely to recognize failures in an early stage and to induce the right treatment choice in case of a reinfection.

2.6. Hematogenous infection as an often-unrecognized cause of recurrent infection after two-stage exchange arthroplasty

An often-unrecognized entity as cause of recurrent infection after successfully treated two-stage exchange arthroplasty: hematogenous infection

Akgün D, Müller M, Perka C, Winkler T.

Arch Orthop Trauma Surg. 2018 Sep;138(9):1199-1206. https://doi.org/10.1007/s00402-018-2972-3. Epub 2018 Jun 5.

Introduction

Reinfection after two-stage exchange arthroplasty is a challenging clinical scenario with limited data on adequate treatment guidelines [39]. It can be due to of either failure to eradicate the previous infection or an infection with a new pathogen [39, 80, 81]. However, the data existing in literature dealing with the latter group is scarce. Beside the possibility of an infection with a new microorganism at the time of reimplantation, a hematogenous spread from another infection focus can play a crucial role. The distinction between both routes is the key in deciding the appropriate treatment option, as patients with an acute infection can be treated successfully with a debridement and implant retention and two-stage exchange in these patients will be an overtreatment with possible worsening of clinical outcomes [15]. The aim of this study was to establish the incidence and characteristics of reinfection due to a hematogenous seeding after a successful two-stage exchange arthroplasty and to raise awareness about this entity to reduce the number of patients, who are erroneously overtreated [39].

Methods

All consecutive treated patients between 2013 and 2015 with a two-stage exchange arthroplasty due to hip and knee PJI (93 hips and 89 knees) were included. Patients were followed up prospectively to identify recurrent infections to identify recurrent infections due to hematogenous spread.

Results

After a mean follow-up of 31.8 months 6% of the patients had a hematogenous reinfection. In all but two cases were the microorganism causing the new infection other than isolated at the time of the initial two-stage exchange. The primary focus could have been identified only in 46% of patients.

Discussion

Hematogenous infection after a successful two-stage exchange arthroplasty is a rare but very important cause of a reinfection. In these cases, debridement and implant retention can be performed with success. Furthermore, it is essential to identify the primary infection source to prevent further treatment failures.

3. Discussion

3.1. Controversy of treatment success in two-stage exchange arthroplasty

Two-stage exchange arthroplasty is furthermore the gold standard for the treatment of chronic PJI in most countries and is practiced almost more than 20 years [45]. However, there is still a very widespread heterogeneity on the reporting success rates in literature. This is based on several facts. First, most of the published studies are designed retrospectively and include patients from a wide range of time interval. Since the diagnosis and especially antimicrobial and surgical therapy of PJI is evolving unexpectedly fast, patients included in these retrospective studies lack mostly a standardized surgical and most importantly antimicrobial treatment algorithms leading to inhomogeneous study cohorts. This can conduce to higher failure rates among the patients with inadequate therapy and thereby alter the overall success rate of the mentioned surgical procedure [55, 59, 82].

Second, there is a lack of an internationally accepted definition of PJI. The most known definitions include Musculoskeletal Infection Society criteria (MSIS) [83], Infectious Diseases Society of America (IDSA) criteria [84] and European Bone and Joint infection Society (EBJIS) criteria [85]. Each definition criteria use different cut off values for diagnostic tests and include or exclude different diagnostic tools in their definition. Although definitive evidence or major criteria for infection are identical between different definitions, the supportive evidence or minor criteria differ and are less agreed upon, which makes the diagnosis difficult especially in patients with low-grade infections [83]. A recent article showed that whereas MSIS and IDSA criteria may miss some patients with PJI (false negative), the proposed EBJIS criteria may be prone to misdiagnose patients who are aseptic as having PJI (false positive), leading to unnecessary surgical interventions and antimicrobial treatment [86]. This variety causes non-comparable study cohorts with different success rates depending on the applied definition.

Third, treatment success after two-stage exchange arthroplasty varies dramatically depending on the criteria used to define success [87]. Although considerable efforts have been made to standardize the definition of PJI treatment success using the Delphi international consensus criteria [88], several problems are frequently encountered. Many patients do not complete the second stage of a two-stage exchange arthroplasty and are not considered in success definitions [45]. The common reasons for not being able to complete the intended reimplantation are patient-related comorbidities and mortality, polymicrobial PJI and patient choice [51]. Every effort should be made to provide the opportunity for reimplantation in every single patient [51]. A further problem is that the microorganism causing the reinfection is mostly different than of the initial causative microorganism [39, 50]. Although this may be considered as success from a microbiological standpoint, the patient still needs to undergo revision surgery due to PJI. Furthermore, attributing mortality to PJI is often subjective and difficult.

Thus, the success rate after two-stage exchange arthroplasty varies significantly between published studies making the results difficult to compare due to limitations mentioned above.

3.1. Impact of causative microorganism on the treatment success

Infecting microorganisms adhere rapidly to foreign material forming biofilms, where they escape from host defense. The role of microbial biofilm in the pathogenesis not only in the context of implant-associated infections but also in many other infections is well studied [14]. Studies analyzing the biofilm resistance have shown that minimal inhibitory concentration of several antibiotics is significantly increased if microbes form biofilms [22]. Thus, antibiotics need to penetrate into the biofilm matrix in order to eradicate infection. Several studies demonstrated high biofilm activity of rifampicin against staphylococcus infections and ciprofloxacin against Gram-negative infections [27-30]. Therefore, pathogens, for which no biofilm active antimicrobial treatment exists, are referred as DTT and include rifampin-resistant staphylococci, fluoroquinolone-resistant Gram-negative bacteria, enterococci and fungi [68]. These microorganisms were associated with higher infect eradication failure rates compared to other more susceptible microorganisms [36, 89, 90]. However recent data shows similar eradication rates in patients with DTT PJI compared to non-DTT PJI, if patients are treated with a two-stage exchange with a long interval (>6 weeks) and receive longer antimicrobial treatment [68, 91]. Based on these findings the term DTT PJI may not be appropriate, since in patients undergoing a two-stage exchange arthroplasty with a long interval no biofilm-active antibiotics are required to achieve good results [92].

Another uncertainty of treatment success exists in streptococcal PJI. It was believed that streptococcal infections are readily amenable to treatment due to high sensitivity to antibiotics. Some studies reported high success rates in streptococcal PJI, even if the prosthesis was retained [64-66]. However other studies showed failure rates as high as 40% in patients with streptococcal PJI [49, 62, 67, 93]. The wide range may reflect various definitions of success used by different studies. Akgün et al. have shown a high failure rate in infect eradication by using a strict definition of treatment success [49]. Citak et al. identified isolation of streptococcus species as an independent risk factor of failure after one-stage exchange arthroplasty [94]. The results of the study by Renz et al. also supported these findings [67]. They showed however, that the administration of long-term suppressive oral antimicrobial treatment was associated with significantly better outcome in streptococcal PJI and suggested to consider it irrespective of surgical treatment.

Thus, the individualization of antimicrobial and surgical therapy regimes enables similar success rates in patients irrespective of causative microorganism.

3.2. The importance of multidisciplinary team approach in the management of PJI

Patients suffering of PJI have mostly poorer health status with severe comorbidities as well as systemic and local compromised immune status due to scar tissue after multiple previous surgeries. This systemic and local immune failure can massively decrease the minimal infecting dose of bacteria and predispose to problems with infect eradication [50]. Akgün et al. have shown a significantly higher risk of treatment failure in patients with a higher Charlson Comorbidity Index [50]. Further studies emphasized the high rate of mortality in patients with high a Charlson Comorbidity Index and host grade after the first stage of two-stage exchange arthroplasty [55, 61]. Thus, medical optimization of these patients is highly recommended both before and during the PJI treatment to enhance our treatment success. Also, Heller et al. recently published a checklist implementing a medical optimization to minimize the risk of postoperative infection, which also can be integrated in two-stage exchange arthroplasty [95]. This is however only possible with a multidisciplinary team approach including infectious disease specialists, internal medicine specialists and orthopedic surgeons, who should be involved in every stage of PJI treatment for each patient.

The role of this multidisciplinary team gets even more important, since the management of patients with PJI does not include only surgical treatment but as importantly adequate antimicrobial treatment to achieve best treatment outcomes. Kilgus et al. recently reported on treating physician dependent causes leading to PJI treatment failure [73]. They identified in 85% of patients with a PJI treatment failure at least one possible reason, which could have been prevented. An inadequate surgical therapy and inadequate antimicrobial treatment were the two most important identified reasons. After an individualized failure analysis, they achieved in their study cohort an infection-free survival of 94.9% with a two-stage exchange arthroplasty. Thus, they recommended a critical review of the failed cases and a multidisciplinary approach by using a checklist algorithm throughout the entire PJI treatment. In another study, Ntalos et al. established a systematic multidisciplinary team approach in the treatment of PJI and assessed its effect on clinical decision-making [75]. Their results showed that performing regular multidisciplinary case discussions led to a significant alteration in the treatment plan, including significant reduction of used antibiotics and number of surgeries performed. This improvement could be explained by a more pronounced consideration and reevaluation of diagnosis and treatment indications in a multidisciplinary team. Consequently, high infection eradication rates could have been achieved in a challenging cohort using a standardized two-stage exchange arthroplasty supported by a multidisciplinary team [79].

3.3. New infection after successful two-stage exchange arthroplasty

Reinfection after two-stage exchange arthroplasty is a very challenging clinical scenario with limited data on adequate treatment suggestions. Some previous studies showed that the pathogens isolated at the time of reinfection were different than the pathogens isolated at the time of initial treatment [50, 81, 96]. The distinction of the route and duration of the new infection is however crucial in the decision-making of the most appropriate treatment. While a perioperative reinfection from the time of the reimplantation with a new microorganism and a longer duration of symptoms (>4 weeks) should be treated with a one- or two-stage exchange arthroplasty, an acute infection mostly due hematogenous seeding with short duration of symptoms (<4 weeks) can be managed with debridement and retention of the prosthesis, which is not as damaging as prosthesis exchange for patients [15, 39]. Most importantly, a possible identification of a primary infection source in patients with a new hematogenous PJI should be performed in order to avoid recurrent hematogenous infections, although it is possible only in a subset of patients [39].

4. Summary and outlook

The aim of this habilitation script was to arm the treating physicians with an armamentarium of knowledge to achieve better success in eradicating PJI. Therefore, the published data concentrated on identification of the factors leading to failure in two-stage exchange arthroplasty in patients with PJI and on optimization of infection-free survival. Microbial biofilm makes the diagnosis and the treatment of PJI more challenging and therefore biofilm-active antibiotics are crucial to enhance treatment success. Microorganisms, for which no biofilm active antibiotic exits, presents a major difficulty in achieving high infect eradication rates in these patients. According to the results of this habilitation script however, an individualization of antimicrobial and surgical therapy regimes with a longer prothesis-free interval and longer antibiotic administration may enable achieving similar success rates in patients irrespective of causative microorganism after two-stage exchange arthroplasty.

Furthermore, the data presented in this habilitation script emphasizes the implementation of a treatment supported by a multidisciplinary team approach as a crucial step to optimize outcome in patients with PJI. It could have been shown, that high infection eradication rates can be achieved by using a standardized two-stage exchange arthroplasty supported by a multidisciplinary team even in a challenging patient cohort.

Given the fact, that there is a wide variety in the definition of PJI and its treatment success, which causes a heterogeneity of existing studies, further research is highly needed on more precisely defining PJI and success. Thus, consistency in definition between studies will enhance the overall quality of existing literature. Especially, when defining treatment success, it is important to distinguish between a new infection and an ongoing infection, as this prevent patients from unnecessary surgical interventions and antimicrobial treatment.

Treatment of PJI in the near future will be more difficult with the increasing age and comorbidities of the patients in the era of rising antimicrobial resistance. Forthcoming studies providing a better understanding of the pathophysiology of PJI on the human body will allow us to correctly identify the infecting microorganisms and their virulence factors and develop newer treatment strategies. Success of our future treatment strategies will depend on improving the indications and technique of our current surgical procedures as well as the biofilm disrupting technologies [97]. Recently it was shown, that enzyme deoxyribonuclease (DNase) can inhibit biofilm formation up to 60 hours and Kaplan et al. were able to show that DNase can increase the sensitivity of the biofilm to antibiotics in an in vivo model [97-99]. Thus, it can be used as preventive biofilm agent in the management of PJI. Furthermore, the use of nanotechnology can help us in disrupting bacterial biofilms. In a study of Iannitelli et al. loaded nanoparticles with antimicrobial agents were able to decrease the stability of the biofilm matrix. As conclusion they stated that adding antibiotics into the nanoparticles can be use against bacterial biofilms [100].

Finally, the field of genomics likely holds the key to a novel diagnostic and treatment approach to infection [97]. With the help of genomics, we can better understand the pathophysiology of PJI, determine biomarkers of infection and so make an early identification with intervention possible. Recently, it has been shown with increasing evidence that micro-RNA (MiRNA) regulation plays an essential role in the immune response to infections and that bacteria such as Helicobacter pylori, Mycobacterium tuberculosis or E. coli alter the expression of specific miRNA patterns in a host organism [101-103]. MiRNAs are small, non-coding molecules consisting about 18-24 nucleotides and have an important role in almost all biological processes. (e.g. stem cell differentiation, apoptosis, bone metabolism and aging processes) [103]. In recent years, the determination of certain miRNA species as diagnostic and prognostic biomarkers in patients with bacterial infections and sepsis has been increasingly applied [101]. At present, there are no published data that have investigated a correlation between certain systemically present miRNA expression patterns and PJI. It can be hypothesized, that the identification of a typical miRNA profile in patients with a PJI could improve the preoperative diagnosis and help treating physicians planning a better treatment strategy, especially in patients with low-grade infections, which mimic an aseptic failure.

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7. Eidesstattliche Erklärung

§ 4 Abs. 3 (k) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité _– Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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Datum Dr. med. Doruk Akgün