Thesis

Catheters as a possible source for complication and infection in hip and knee arthroplasty patients. A retrospective study.

submitted by

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Graz, 27.01.2023

Declaration of Academic Integrity
I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, January 27th, 2023, Elias Georg Hader eh.

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Glossary

PJI…periprosthetic joint infection(s)
THA…total hip arthroplasty
TKA…total knee arthroplasty
PVC…peripheral venous catheter(s)
CVC…central venous catheter(s)
IDC…indwelling bladder catheter(s)
ICU…intensive care unit(s)
BSI…blood stream infection(s)
CABSI…catheter-associated blood stream infection(s)
UTI…urinary tract infection(s)
RKI…Robert-Koch-Institution
KRINKO…Commission for Hospital Hygiene and Infection Prevention
CoNS…coagulase negative staphylococci
MRSA…methicillin-resistant staphylococcus aureus
MSSA…methicillin-sensible staphylococcus aureus
OR…odds ratio
Etc…etcetera
CRP…C-reactive protein
ESR…erythrocyte sedimentation rate
WBC…white blood cell count
AAOS… American Association of Orthopaedic Surgeons
CT…Computed Tomography
MRI…Magnetic Resonance Imaging
Hb…Haemoglobin
PCA…patient controlled analgesia

Zusammenfassung

Einleitung Gelenksersatzoperationen, insbesondere jene des Hüft- und Kniegelenks, zählen zu den häufigsten Operationen in Österreich. Eine Reduktion von Risikofaktoren ist daher wichtig, um potenzielle postoperative Komplikationen zu vermeiden. Eine seltene, aber gefürchtete Komplikation ist eine Protheseninfektion. Ein möglicher Risikofaktor für Infektionen sind peripher venöse Katheter (PVK). Ziel der Studie ist es, einen möglichen Einfluss eines vermehrten Einsatzes von peripheren venösen Kathetern auf postoperative Komplikationen darzustellen.

Methoden Für diese Studie wurden Patient*innen, welche sich einer Gelenksersatztherapie des Knies oder der Hüfte an der Universitätsklinik für Orthopädie und Traumatologie, Medizinische Universität Graz, Österreich, im Zeitraum Juni bis August 2021, unterzogen, inkludiert. Ab dem Zeitpunkt der Operation, erfolgte ein 3-monatiger Follow-up Zeitraum, in welchem Komplikationen jeglicher Art erfasst wurden, welche in diesem Zeitraum auftraten. Des Weiteren wurden Daten des stationären Aufenthalts sowie der Operation erfasst, welche einen Risikofaktor für weitere Komplikationen darstellen können.

Ergebnisse Insgesamt wurden 219 Gelenksersatzoperationen bei 215 verschiedenen Patient*innen durchgeführt, davon waren 124 weiblich (124/215, 57,67%) und 91 männlich (91/215, 42,33%). Das Durchschnittsalter zum Zeitpunkt der Operation war 69,55 Jahre, mit einem Minimum von 27 und Maximum von 90 Jahre. In 218 Fällen wurden peripher venöse Katheter (PVK) verwendet. Patient*innen hatten durchschnittlich für 5,5 Tage einen PVK gelegt. Komplikationen mit einer engen Beziehung zur Katheter Verwendung wurden 90-mal (90/219, 41,1%) dokumentiert. Sechzehn (16/90, 17,78%) dieser 90 Komplikationen waren infektiöser Genese. In der Follow-up Periode wurden insgesamt 69 Komplikationen (69/219, 32%) erfasst. Sechsunddreißig (36/69, 52,2%) dieser Komplikationen wurden als leicht eingestuft, 15 (15/69, 21,7%) als moderat und 18 (18/69, 26,1%) als schwerwiegend. Es wurde eine leichte Korrelation zwischen dem vermehrten PVK-Einsatz und erhöhter Komplikationsrate festgestellt ($p=0,031$, $r=0,133$).

Schlussfolgerung In unserer Studie zeigt sich eine erhöhte Komplikationsrate bei vermehrtem PVK-Einsatz. Dieses Ergebnis spricht gegen den Einsatz eines PVK zur parenteralen Medikamentengabe. Bei richtiger Indikation sind orale und parenterale

Applikation gleich wirksam. Insbesondere bei analgetischer Medikation zeigt eine frühzeitige Umstellung auf orale Therapie sogar Vorteile für Patient*innen. Studien haben gezeigt, dass die Implementierung von internen Guidelines oder digitalen Unterstützungssystemen die frühzeitige und korrekte Konversion von parenterale auf orale Medikation fördern kann.

Abstract

Introduction Joint replacement surgeries, especially those of the hip and knee joints, are among the most frequent operations in Austria. Reducing risk factors is therefore important to avoid potential postoperative complications. A rare but feared complication is a periprosthetic joint infection. Peripheral venous catheters (PVCs) are a possible risk factor for infections. The aim of the study is to show a possible influence of an increased use of PVCs on postoperative complications.

Methods For this study, patients who underwent joint replacement of the knee or hip at the Department of Orthopaedics and Traumatology, Medical University of Graz, Austria, in the period from June to August 2021 were included. Starting with the time of surgery, a 3-month follow-up period was conducted in which complications of any kind occurring during this period were recorded. Furthermore, data on the inpatient stay and the operation were recorded, which could represent a risk factor for further complications.

Results A total of 219 joint replacement operations were performed on 215 different patients, of which 124 were female (124/215, 57.67%) and 91 were male (91/215, 42.33%). The average age at the time of surgery was 69.55 years, with a minimum of 27 and maximum of 90 years. Patients had a PVK in place for an average of 5.5 days. Complications closely related to catheter use were documented 90 times (90/219, 41.1%). Sixteen (16/90, 17.78%) of these 90 complications were of infectious origin. A total of 69 complications (69/219, 32%) were recorded during the follow-up period. Thirty-six (36/69, 52.2%) of these complications were classified as mild, 15 (15/69, 21.7%) as moderate and 18 (18/69, 26.1%) as severe. A slight correlation was found between increased PVC use and increased complication rate ($p=0.031$, $r=0.133$).

Conclusion

Our study shows a higher complication rate correlating with increased use of PVC. This result speaks against the use of a PVC for parenteral drug administration. With the right indication, oral and parenteral administration are equally effective. Especially in the case of analgesic medication, an early switch to oral therapy even shows advantages for the patient. Studies have shown that the implementation of internal guidelines or digital

support systems can promote early and correct conversion from parenteral to oral medication.

1 Introduction

Operations on the musculoskeletal system are one of the most common operations nowadays. One major part of these musculoskeletal operations is the arthroplasty (2). Arthroplasty is a surgical procedure, where the function of a joint is restored. An artificial joint may therefore be used. This procedure has a good clinical outcome in most cases. However, due to the increasing number of these operations, the number of complications raises as well (3).

A periprosthetic joint infection (PJI) is a dreaded complication that almost always means another surgical intervention. Particularly problematic in the case of infection, is the ability of microbes to form a biofilm on artificial surfaces of a prosthesis, which reduces the effectiveness of antibiotics on the microbes (4). This results in a more difficult and prolonged therapy. Therefore, the most important protective factor against potential infectious complications, is the reduction of risk factors (5).

There is one possible source of infection, which is not yet considered to be of major importance in prevention. Catheters that remain in the human body for a long time, whether intravascular, urinary or any other kind of catheter, always offer a potential entry point for pathogens (6). Despite the known risk of infection and other adverse effects occurring due to the use of catheters, postoperative drug therapy often remains being administered intravenously over a prolonged period.

1.1 Definition

1.1.1 Arthroplasty

An arthroplasty is an artificial replacement of a joint. Usually, a joint is artificially replaced, when there is pain or loss of function due to age-related degeneration. It requires particularly strict indication, since the resection of the joint surfaces is final and irreversible (7). The implantation of a prosthesis is intended to provide long-term relief from symptoms (8). Likewise in the case of congenital deformities, chronic inflammations, or substance defects in the bone (for example, in the context of a malignant process or

osteoporosis), an arthroplasty can be installed to prevent further complications and alleviate symptoms. Conservative therapy attempt is necessary prior to surgical procedure (9).

Depending on the indication, a total arthroplasty or partial arthroplasty can be fitted. In the case of total arthroplasty, for example total hip arthroplasty (THA) or total knee arthroplasty (TKA), the entire joint is artificially replaced, while in the case of partial arthroplasty the joint is solely replaced in some extent. In case of partial hip arthroplasty, the femoral head and neck is replaced while the Acetabulum remains unaffected. A common indication for this prosthesis is a fracture of the femoral neck. Unicompartmental arthroplasty is used in knee arthroplasty, when one of the two condylus femoris is damaged. It can also be used in case of an isolated patellofemoral gonarthrosis (7). The prosthesis can then be implanted without or with the help of a special bone cement (10).

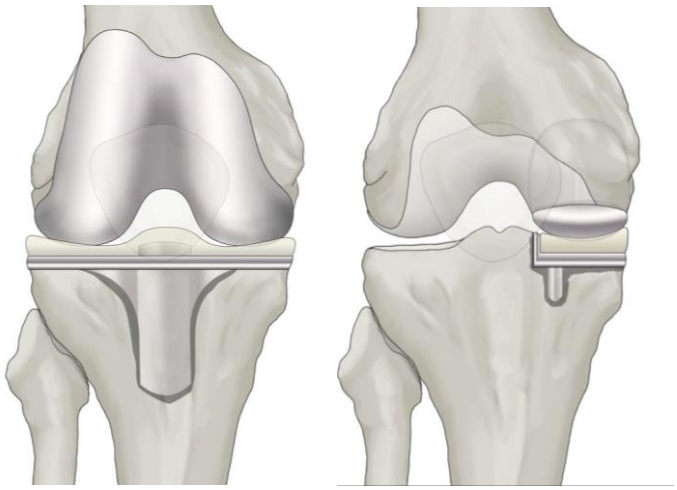

Figure 1 shows a total knee arthroplasty (TKA) on the left versus a unicompartmental knee arthroplasty on the right. Source: Operative Verfahren der Unfallchirurgie/Orthopädie (10)

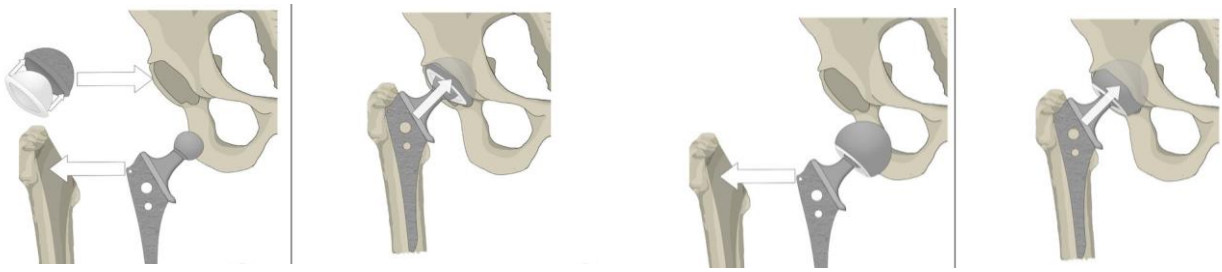

Figure 2 shows the process of implantation of a total hip arthroplasty (THA) on the left versus partial hip arthroplasty on the right.

Source: Operative Verfahren der Unfallchirurgie/Orthopädie (10)

1.1.2 Catheter

A catheter is a flexible and tubular object that is inserted into a vessel, hollow organ or body cavity. It is used to deliver fluids into or out of the body (11).

Peripheral venous catheters (PVC) are intravascular catheters that are inserted in peripheral veins. They are usually placed in the elbow, at the forearm or at the back of the hand (12).

Central venous catheters (CVC) are also intravascular catheters, whereby the catheter tip is advanced into the superior or inferior vena cava. Access via the jugular vein or the subclavian vein is typical. The insertion of a CVC is indicated when frequent administration of drugs or infusions is expected, parenteral nutrition is required, central venous pressure monitoring is needed, pulmonary artery access is necessary or the venous status does not permit the insertion of a PVC (13). Also the use of drugs with toxic effects on the veins requires insertion of a CVC (14).

An indwelling bladder catheter (IDC) can be inserted by a suprapubic access or through the urethra. The transurethral approach is the more common. Insertion of such a catheter is indicated for acute urinary retention, voiding disorders, measuring the water balance and also perioperative (15). A transurethral IDC is a frequent cause of nosocomial urinary tract infections (16).

1.1.3 Drainage

Drains are used to reduce the accumulation of fluids after an operation. In primary hip and knee arthroplasty, it is very common to use drains. Aim is to reduce the risk for haematoma and infection. However, the risk for increased postoperative blood loss remains (17). Reducing the risk for infection and haematoma are considered as prophylactic indications. Drains can also be used for diagnostic observance, drain of fluid accumulation or to alleviate symptoms. Other complications of drainage include mechanical irritation, pain, maceration of the skin and infection. A common used drain at the Department of Orthopaedics and Traumatology is the Redon drain (18). However, the positive effect of a drain is disputed. Benefit of a drain after TKA or THA is not yet proven, further studies are therefore required. Thus, a prophylactic indication of drain is not recommended (19). The benefit of using drain can vary, depending on the patient, wound and procedure (1). Studies have also shown that the use of drain after hip or knee arthroplasty, had no significant effect on the postoperative infection rate. Rate of haematoma can be significantly reduced by using drains. On the other hand, using drains increases the risk for patient needing transfusions due to anaemia (17).

1.1.4 Biofilm

PJI is often caused by microorganisms that are able to form a biofilm. Bacteria have certain structures which help them attach to other surfaces. Those structures are called adhesins (20). If these microorganisms colonize the prosthesis, they start to form an extracellular matrix in which the bacteria settle. They transform from a planktonic form, which means they can move around, to a stationary from (3, 21). Furthermore, the metabolism of the bacteria is reduced and they divide less. Due to the extracellular protection, which is provided by the matrix, the reduced number of divisions and the production of inactivating enzymes, these microbes become less sensitive to antibiotics and are also better protected against immune response (3, 4, 20). After colonisation, the bacteria begin to form a multi-layered biofilm. The "immature" biofilm continues to grow until a more stable matrix has developed, this is then referred to as a "mature" biofilm. The development of a mature biofilm can take from a few days to several weeks (3, 21). Once colonized, the bacteria can also remain quietly for a long period of time. An occurrence, like a decreased host immune activity, can then enable the bacteria to overgrow and induce the clinical manifestation of a

PJI (20). Once a medical device in infected, it can also be the source for further dissemination and can result in a chronic infection (22).

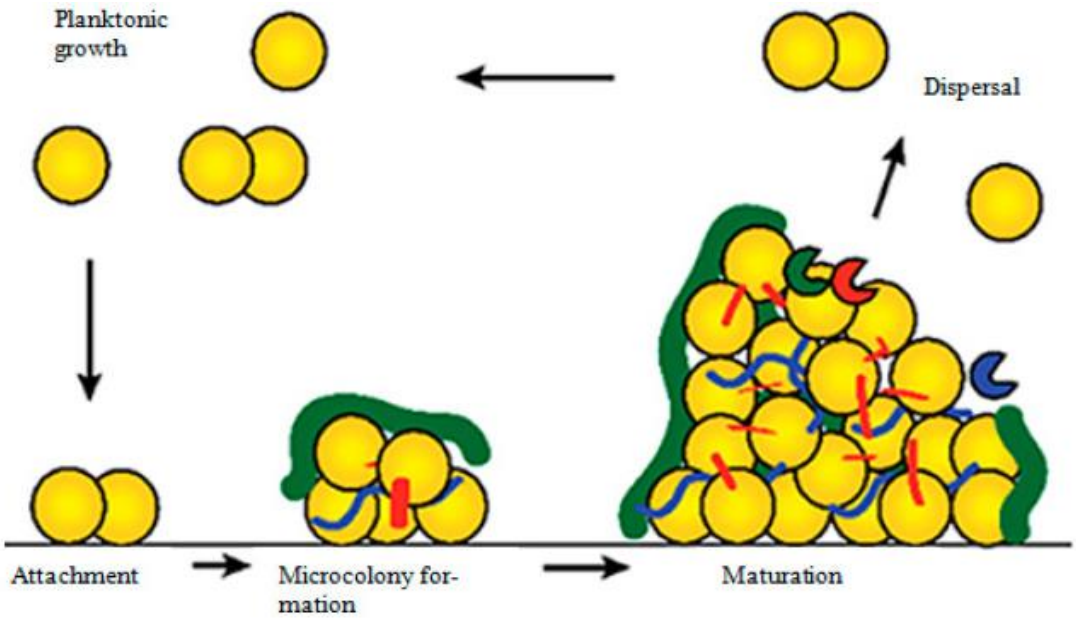

Figure 3 displays the genesis of a bacterial biofilm on a medical device and further dissemination of bacteria.

Source: Non-Antimicrobial Adjuvant Strategies to Tackle Biofilm-Related Staphylococcus aureus Prosthetic Joint Infections by Pant et al. (22)

1.2 Epidemiology and Economy

1.2.1 Arthroplasty, PJI and surgical site Infection

Surgical procedures are part of everyday life in hospitals. According to Statistics Austria, there were over 1,280,000 operations throughout Austria in 2019. This accounted for 28% of all therapeutic services provided over the course of an inpatient stay in a hospital in 2019. Most of these surgical interventions concerned the musculoskeletal system (23.85%) (2). A large proportion of orthopaedic interventions involve joint replacement of the hip or knee (23).

In 2020, according to the Federal Ministry, there were 981 136 operations with an inpatient setting. Of these operations, 17 493 were THA (1.78%) and 15 207 were TKA (1.55%). THA and TKA together accounted for a total of 32,700 operations, which makes up 3.33%

of all inpatient operations. Partial arthroplasty is not included in this statistic. However, the data from 2020 must also take into account the slump caused by the COVID-19 pandemic (23).

In a retrospective study by Leitner et al, all hip and knee replacement surgeries in Austria from 2009 to 2015 were analysed. According to this data, Austria is among the leaders on an international level, concerning the amount of hip and knee replacement surgeries undertaken. In 2014, Austria was able to show the highest number of implanted knee arthroplasty (TKA) in a comparison with other OECD countries. Only Switzerland and Germany can provide similarly high numbers of interventions (24).

In 2007, a study by Kurtz et al evaluated the quantity of joint replacement procedures in the USA and calculated a prediction for future numbers. Between 2005 and 2030, an increase in numbers of 137% to 301% in hip or knee arthroplasty was projected (25). On the website of the Swiss national registry for hip and knee replacement, one can also see a clear increase in hip and knee replacement procedures in Switzerland that continuous until 2021 (26). It is likely that the number of operations in Austria is increasing as well, similarly to the numbers in Switzerland or the USA. Due to the large number of hip and knee prosthesis implanted each year and the growth of that number, the amount of surgery related complications and revision surgeries raises as well. (24).

Primary implants are estimated to have a periprosthetic joint infection rate of 1-2.5%, with an even higher rate of infection in revision surgery. Occurrence of PJI means a financial loss of 40,000 € to 50,000 € or even more per infection for the healthcare system. This amount also includes the loss of earnings (21, 27, 28).

Generally, hospital-associated infections have become the leading complications of modern surgery. Surgical site infections are the most common kind of infection. Surgical site infections have therefore become the main reason for hospital readmissions and are accountable for the greatest economic burden of all healthcare associated infections (1).

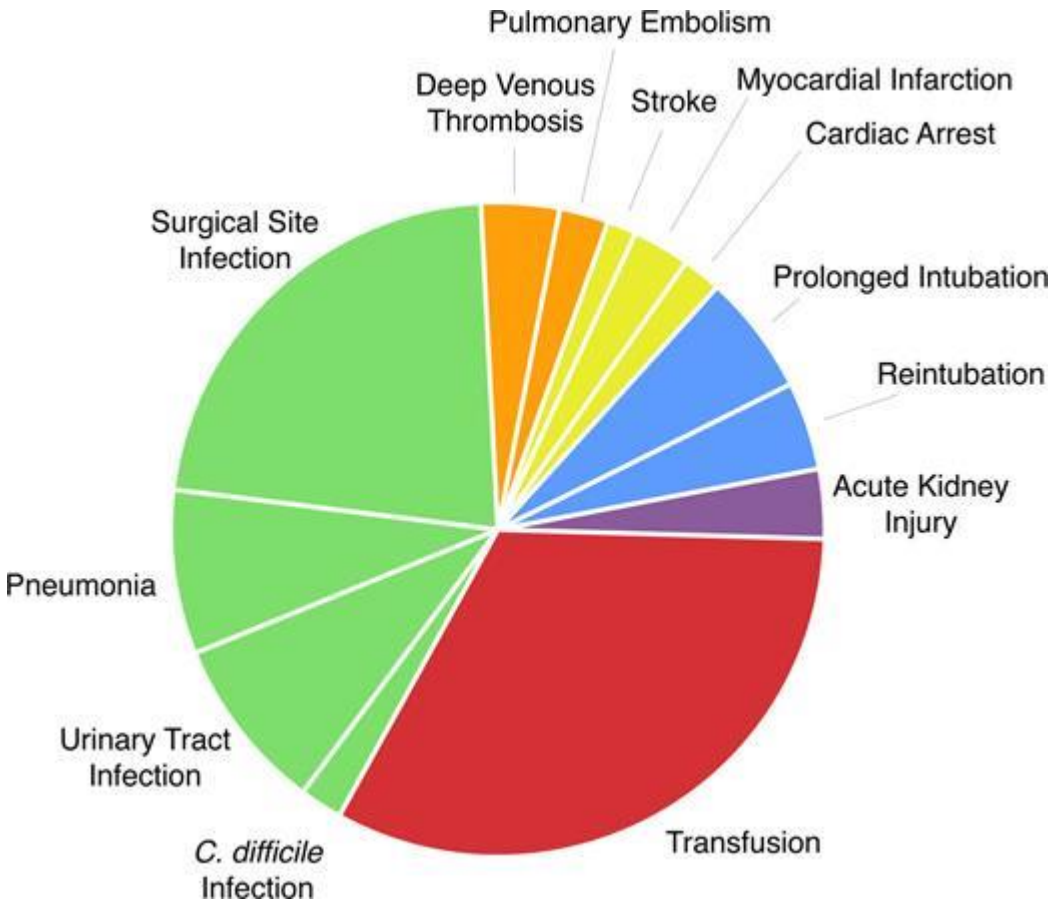

Figure 4 shows a pie chart, representing the most common adverse perioperative events. Green represents the hospital associated infections. A surgical site infection is the most common infection and solely second to transfusions, when looking at all possible adverse events.

Source: Emerging Paradigms in the Prevention of Surgical Site Infection: The Patient Microbiome and Antimicrobial Resistance (1)

1.2.2 Catheters and catheter-associated Infections

PVC accounts for one of the most used devices in our medical system. In the USA 200 million PVC are inserted each year, compared to about 300 million inhabitants. In Europe, the stats are similar (29). Worldwide, it is estimated that 1,2 billion PVC are used each year (30).

However, the number of intravascular catheters used, does not necessarily match with the number of intravascular catheters needed in clinical setting. A study of 17,000 patients in Germany found, that one in three had a central or peripheral catheter with only 46% of these catheters still in active use (31). In Emergency departments, a 'just in case' PVC is inserted regularly. 32,4% of these 'just in case' PVC remain unused for at least 24 hours

(32). About 36% - 42% of all PVC are removed because of failure. Statistically 226,2 PVC failures occur/1000 days of use (33, 34).

Infections are a rather sever adverse effect of catheter use. With intravascular catheters in place, an infection occurs in 3%, most of which are limited to local infections (31). This differs depending on the type of catheter and whether it is a normal bed ward or an intensive care unit (ICU). Approximately 60% of all nosocomial infections are triggered by a catheter placed in a blood vessel, with a CVC posing the highest risk of infection (6). When looking at the adverse effects of intravascular catheters, a bloodstream infection (BSI) is probably the most severe complication. Using a PVC, the overall risk for BSI is 0.5 BSI/1000 days and with a CVC, this rate increases to 2.7 BSI/1000 days (35). In non-intensive care patients, the infection rate is greatly reduced to 0.19 PVC-BSI/1000 days and 0.18 CVC-BSI/1000 days (36).

Risk for infection is increased for patients being treated on the ICU. BSI occurs in 9.5% of all ICU patients, with a median time to onset of BSI of 9 days. Epidemiologically, there are 10.3 ICU BSIs/1000 days (37). In ICU-BSI due to persisting PVC, the number of infections is about 2.41-5.33 ICU-BSI/1000 days (6, 38).

In the case of a catheter-associated bloodstream infection (CABSI) with subsequent treatment in the intensive care unit, costs increase by an additional 3,600 € -29,900 € per BSI (39-41). In literature, these additional costs vary depending on the BSI being associated with a PVC or CVC. Tacconelli et al valued the additional incurred costs due to CVC related CABSI during intensive care unit stay at 35.9 to 163.9 million Euros per year. Costs vary depending on the country the study was conducted in (39).

Another frequently used and placed catheter is the IDC. 12-16% of hospital inpatients receive an IDC in the course of their stay. 80% of urinary tract infections (UTI) can be attributed to colonisation of the urinary catheter. Urinary tract infections (23.2%) are among the most frequent nosocomial infections, together with postoperative wound infections (24.3%) and lower respiratory tract infections (21.7%) (16). In the USA, it is estimated that additional costs of 600 - 4700 US dollars can be incurred per catheter associated UTI (42, 43).

Costs nowadays may have changed in comparison to the numbers evaluated by the studies above.

1.3 Causative Pathogens

1.3.1 Microbes in PJI

There are many different microbes which can cause a PJI. However, the most common pathogen, is the *staphylococcus aureus* (22%-27%) followed by *coagulase-negative staphylococci* (*CoNS*) (14%-22%) and *streptococcus species* (4,4%-14%). Aerobic gram-positive bacteria make up 47,6%-65% of all PJIs. A polymicrobial infection is the case in 13,8% of all hip PJIs and 4,4% of all knee PJIs (21, 44).

Methicillin-resistant staphylococci are at cause for 21% of all PJIs. 40% of the *staphylococcus aureus* and 76% of the *CoNS* were methicillin-resistant (44). A *MRSA* infection shows a different prognosis than *MSSA* infection and requires other antibiotic therapy. Mortality rate is significantly higher in *MRSA* associated BSI than in BSI caused by *MSSA* (OR 1,93) (45).

1.3.2 Microbes in catheter-related Infections

Bacterial colonization of catheters is a common occurrence. According to a study by Blanco-Mavillard I. et al, 5,8% of all PVC inserted yielded positive microbiological growth on the catheter. When the site of insertion showed signs of infection, 53,6% of the catheters were positive for bacterial growth. The most common pathogen was *Staphylococcus epidermidis* (70,7%), followed by *Staphylococcus aureus* (4,9%) and *Staphylococcus hominis* (4,9%) (33).

CoNS were the most frequent pathogen in BSI associated with CVC and PVC. The infection with *CoNS* occurred 1,57 times more often in CVC than in PVC. *Staphylococcus aureus* and *Enterobacteriae species* are 2,5 times more often found in PVC-BSI (46). Other studies identified *Staphylococcus aureus* as the most common pathogen responsible for PVC-BSI (53%) and CVC-BSI (33%) (36).

Patients on the ICU with suspected CVC-BSI show a different pattern of pathogens. *Staphylococcus aureus* growth was found in 50% of the cases with BSI. Other pathogens

were *Enterococcus faecalis* (41,2%), *Acinetobacter baumannii* (38,2%), *Klebsiella pneumoniae* (32,4%) and *Pseudomonas aeruginosa* (20,6%) (47).

The type of bacteria responsible for the infection, also affects the clinical outcome. A *Staphylococcus aureus* bacteraemia shows a higher rate for complicated BSI and a higher mortality rate (OR 1,49-1,93) (36, 45, 48).

The most common pathogen in catheter-associated UTI is *Escherichia coli* (43,6%), followed by *Enterococcus species* (23%), *Pseudomonas aeruginosa* (10,7%), *Klebsiella species* (10,3%) and *Proteus species* (9,6%). *Staphylococcus aureus* is just at cause for 3,2% of all catheter-associated UTI (16).

1.4 Clinical Manifestation

1.4.1 Symptoms of catheter-related Infection

The most frequent PVC failure is occlusion or infiltration (23%). An infection of the PVC and superficial venous system, in medical terms referred to as thrombophlebitis, occurs to 12% of all PVCs. Dislodgement of PVC happens in 7% of catheters (34).

Typical symptoms of an infection are rubor/redness, dolor/pain, calor/heat, tumor/swelling and functio leasa/loss of function (49).

A thrombophlebitis shows typical symptoms of an infection. In addition, a hard strand may be palpable as a thrombosis may develop. Due to a vena perforans, a conduction of the infection into the deep venous system is possible. However in most cases, no severe complication originates due to this infection (50).

While the infection of a PVC is mostly limited to a local infection, a CVC infection results in BSI far more often (35). Typical symptoms of a BSI are fever, chills, accelerated heartbeat and oliguria. 50% of all PVC associated BSI, also show a thrombophlebitis (41).

An UTI is common with present urinary tract catheter. It favours the formation of an UTI in female, as well as male patients. Typical symptoms are dysuria, pollakisuria, alguria and haematuria. Incontinence and suprapubic pain can also be manifestations of an UTI. A

possible complication is the ascension of the infection. This can result in upper urinary tract infection and pyelonephritis (51, 52).

1.4.2 Symptoms of PJI

Every case of potential PJI should be treated as one, until the contrary has been proven. Typical infection signs can be detected in physical examination. Depending on the time from surgery to the occurrence of symptoms and the type of symptoms, the PJI can be separated in 4 categories. Symptoms of acute infection like redness, swelling, pain and warmth and maybe systemic infection signs, indicate an acute infection. If these signs appear inside 3 months after the operation, it is classified as acute infection. After 3 months, it is classified as delayed acute infection. A persisting purulence inside 3 months after operation, may indicate an early chronic infection. A chronic infection usually appears after 3 months. Symptoms of such may be a present sinus, persisting pain or loosening of the prosthesis (53).

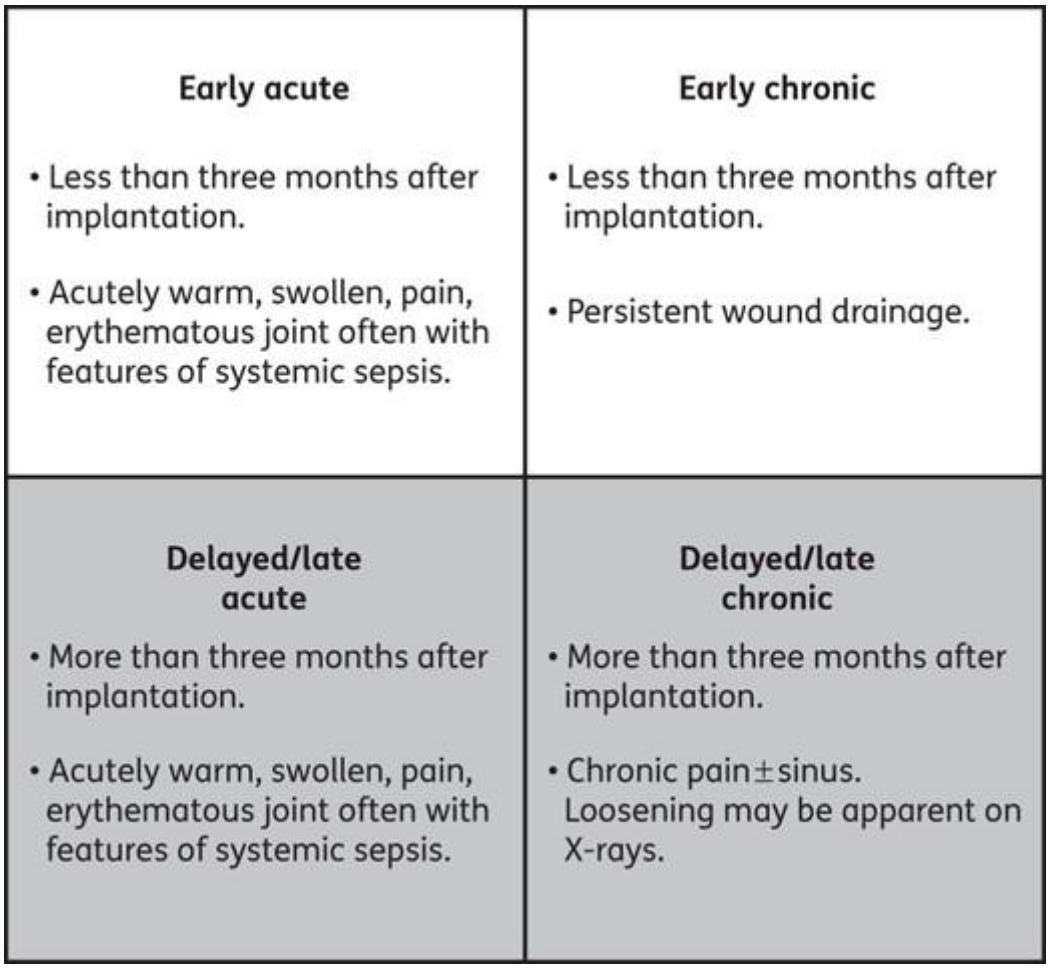

Figure 5 gives an overview of the classification of the PJI depending on symptoms and time

Source: The clinical presentation of prosthetic joint infection (53)

Patients with PJI often have episodes of increased pain during the night or at rest. Also, PJI often causes postoperative wound healing problems and prolonged secretion of the wound (3). A slight redness of the surgical wound may indicate a PJI, however this is no certain sign for an infection. Solely a discreet pink colour of the wound, as seen in the right picture of figure 4, makes a PJI unlikely (54). Fever, chills and fatigue are unspecific signs of a PJI. However, these symptoms should be considered as signs of a PJI, if an arthroplasty is recorded in the medical history (55). The only definitive sign of PJI is the presence of a sinus tract or purulence around the prosthesis, as pictured in Figure 4 (56).

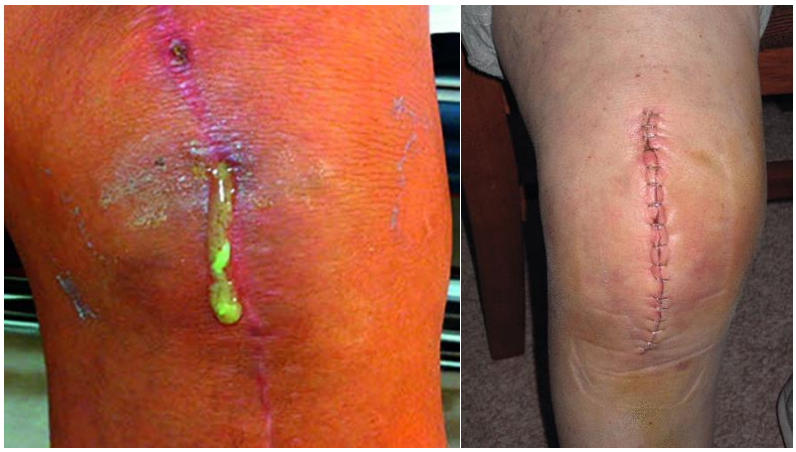

Figure 6 pictures purulence flowing out of an operation scar indicating a definitive PJI on the left while the right picture shows solely a slight pink colouring of the operation scar which makes a PJI unlikely.

Source: The management of prosthetic joint infection in the community: a guide for general practice (54).

1.5 Diagnosis

Essential for the right treatment, is the right diagnosis. To avoid an incorrect, maybe even harmful treatment, it is important to differ between multiple possible differential diagnoses. When signs of infection occur, there needs to be clearance if the infection also applies to the prosthesis or is solely limited to the surface. When there is persisting pain and swelling, it could, for example, be a PJI or an aseptic loosening of the prosthesis. Therefore, a precise diagnosis is important. The most accurate process of diagnosing PJI includes laboratory, microbiology, histology and diagnostic imaging (56).

In 2018, new diagnostic criteria were established by Parvizi et al., which represented a consensus rather than evidence-based algorithm. In comparison to the 2011 Musculoskeletal Infection Society criteria, the sensitivity raised from 86,9% to 97,7% and specificity from 79,3% to 99,5% (57, 58).

There are major and minor criteria for the diagnosis of PJI. 2 positive cultures of the same organism or the presence of a sinus tract communicating with the prosthesis is defined as a major criterion. Preoperative and intraoperative minor criteria are evaluated with 1 to 3 points. A score of 6 points or more is defined as infected, 4-5 is inconclusive and 3 or less is defined as not infected. An intraoperative score of 6 or more is defined as infected, 4-5 as inconclusive and less than 3 as not infected. If the preoperative score is indecisive,

intraoperative criteria can be added to diagnose PJI. In case the intraoperative score is inconclusive, further molecular diagnostic steps can be used (57, 58).

Major criteria (at least one of the following)	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

		Minor Criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP *or* D-Dimer	2	≥6 Infected
		Elevated ESR	1	
	Synovial	Elevated synovial *WBC count or LE*	3	2-5 Possibly Infected [a]
		Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

	Inconclusive pre-op score *or* dry tap [a]	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	4-5 Inconclusive [b]
	Positive purulence	3	
	Single positive culture	2	≤3 Not Infected

Figure 7 visually represents the scoring system which may be used to diagnose a PJI.

Source: Parvizi et al, 2019 (57)

Preoperative criteria are an elevated C-reactive protein (CRP) (>1 mg/dl) or D-Dimer (860 ng/ml) (2 points), elevated erythrocyte sedimentation rate (ESR) (>30 mm/h) (1 point), elevated synovial white blood cell (WBC) count (>3000 cells/µl) or leucocyte esterase (LE) (3 points), elevated synovial alpha-defensin (3 points), elevated polymorphonuclear percentage (PMN) (>80%) (2 points) and elevated synovial CRP (>6,9 mg/l) (1 point). Intraoperative criteria are intraoperative positive histology (3 points), positive purulence (3 points) or a single positive culture (2 points) (57, 58).

1.5.1 Preoperative Screening

When the suspicion of PJI is present, testing the blood for specific markers can be useful to rule in or rule out a PJI. For the biomarkers C-reactive protein (CRP), erythrocyte

sedimentation rate (ESR) and Interleukin-6 (IL-6), a strong recommendation exists. A meta-analysis by Kai Xie et al. rated IL-6 as a good serum marker for PJI. Especially in low-grade infections, IL-6 is a good marker with a sensitivity of up to 0,80 (59). Even though IL-6 is as reliable as the other parameters, IL-6 is not as good available as the others, according to the American Association of Orthopaedic Surgeons (AAOS) (60).

When testing for biomarkers, the combination of CRP and ESR were strong at ruling out or ruling in a PJI. When testing for CRP, the sensitivity is 0,90 - 0,94 and specificity is 0,78 - 0,83. The sensitivity and specificity for ESR alone is 0,81 - 1,00 and 0,56 - 0,87. When both, ESR and CRP are positive, the sensitivity raises to 0,94, however the specificity decreases to 0,77 (21, 61).

CRP and ESR have limited diagnostic value in patients requiring reimplantation, those with inflammatory diseases, and during the early postoperative period. The CRP level usually peaks on postoperative day 2 and falls back to normal levels 2 to 3 weeks later (58). Missing elevation of CRP and ESR do make an infection unlikely, however it is possible that still an infection is present, for example in low-grade infections (5).

Even though D-Dimer is a recommended biomarker in the 2018 guidelines, it is not used in the routine diagnose process of PJI. One reason could be, that there is no standardization in measurement of the D-Dimer. Different assays are used with about 20 different monoclonal antibodies, which all have different specificity. Therefore D-Dimer is not a useful parameter, according to Moser et al (62).

Another serum marker not used in the 2018 criteria, is procalcitonin. It is usually used to detect bacterial infection. However, procalcitonin peaks inside 6 to 24 hours when an infection is present and decreases to normal levels earlier than CRP. In addition, the procalcitonin of patients with local infection overlaps with the normal range of procalcitonin a lot of times. Therefore, the use of procalcitonin for detection of PJI has a very low specificity and therefore is not useful (58).

1.5.2 Joint Aspiration

The punctuation of a joint and aspiration of the synovial fluid is the most accurate parameter for ruling in a PJI. Even low-grade-infections can be detected with the synovial

fluid. Different authors use different cut-off points for the different test to be rated as positive. A test for total synovial leucocyte count or percentage of polymorphonuclear cells is classified as positive, if the leucocyte cell count is above 2000-3000 cells/µl or 70%-80% of the total cell count is made up of neutrophil granulocytes. This test can be false positive when a rheumatic disease or chronic instability is present (3, 57). Generally, the sensitivity and specificity for aspiration is 80% vs 94% (63).

PCR can also be used to identify pathogens in the synovial fluid, showing a sensitivity and specificity of 84% and 89%, respectively (56).

Another promising marker in synovial fluid is alpha-defensin. Alpha-defensin is a peptide, which is produced from neutrophil granulocytes in the presence of bacterial infection. There are different methods of measuring alpha-defensin. Enzyme-linked Immunosorbent Assay (ELISA) and Alpha Defensin Lateral Flow (ADLF) can be used. It is debated, which test is more reliable. Values for sensitivity and specificity of alpha-defensin are disputed. Most studies agree on a high specificity (99%). Sensitivity is assumed to be at 54%-97%. Routine testing for alpha-defensin is not recommended due to its potential low sensitivity. Though it can be used as confirmatory test, when synovial fluid leukocyte count is not readable because of the high specificity (56, 58).

1.5.3 Microbiology

Golden standard in the process of diagnosing a PJI, is a tissue sample with histological and microbiological analysis of suspicious areas. Material for the microbiological analysis can be obtained by aspiration of synovial fluid, gathering tissue sample or of the prosthesis surface. 3-6 samples of different areas should be obtained (28).

2 or more positive cultures are a very good test to rule in an PJI, however inconsistent for ruling out (60). When 3 or more positive samples are obtained, the probability of the presence of an infection goes up to 90% (21). The culturing of multiple intraoperative tissue samples is strongly recommended by the AAOS (60).

When using the method of aspiration, a negative sample does not rule out a PJI since bacteria, which has colonised the prosthesis and is surrounded by a biofilm, is not detected (3). Culture of synovial fluid shows a sensitivity of 45%-79% and a specificity of 95%-

99% (56). The use of gram-stain is a fast method for diagnosing the presence of pathogens. Even though the specificity is high (>90%), the sensitivity is very low (10% - 30%) (28).

When obtaining microbiological samples, antibiotic therapy needs to be paused 14 days prior to the collection of the samples. When antibiotics are used in this period of time, the rate of false negative test raises to 55% (60). However, the need to pause the antibiotics, does not apply in life-threatening situations. Also if no PJI is suspected, an antimicrobial therapy prior to revision surgery is indicated (64).

Other reasons for missing bacterial growth could be errors in the process of collecting samples, long transport time, low bacterial density or low virulent pathogens (28).

1.5.4 Histology

Histological samples of tissue, synovial fluid or sonicated fluid is good for ruling in a PJI (60). In histological examination, the cell count of neutrophil granulocytes is decisive for the test to be valuated as positive. It was shown, that the number of neutrophil granulocytes in the periprosthetic tissue correlates with the presence of PJI (58). A greater number than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification, is counted as a positive histological examination (58). Sensitivity and specificity is 80%-98% versus 92%-99% (3, 28, 56).

1.5.5 Diagnostic Imaging

Diagnostic imaging can help with diagnosing a PJI, however it is not part of the criteria developed by Parvizi et al (57).

Radiograph images may indicate an infection, but it is not sensitive nor specific enough to diagnose a PJI. Radiograph images can be used to compare them to previous radiographic images, so periprosthetic changes can be detected. However, to differentiate between septic and aseptic complication with solely using radiograph images, is very difficult (21, 56, 58). Radiolucent lines, focal osteolysis, periosteal bone formation or early loosening may all suggest PJI (65). Still, radiograph images are recommended for diagnostic procedure (5).

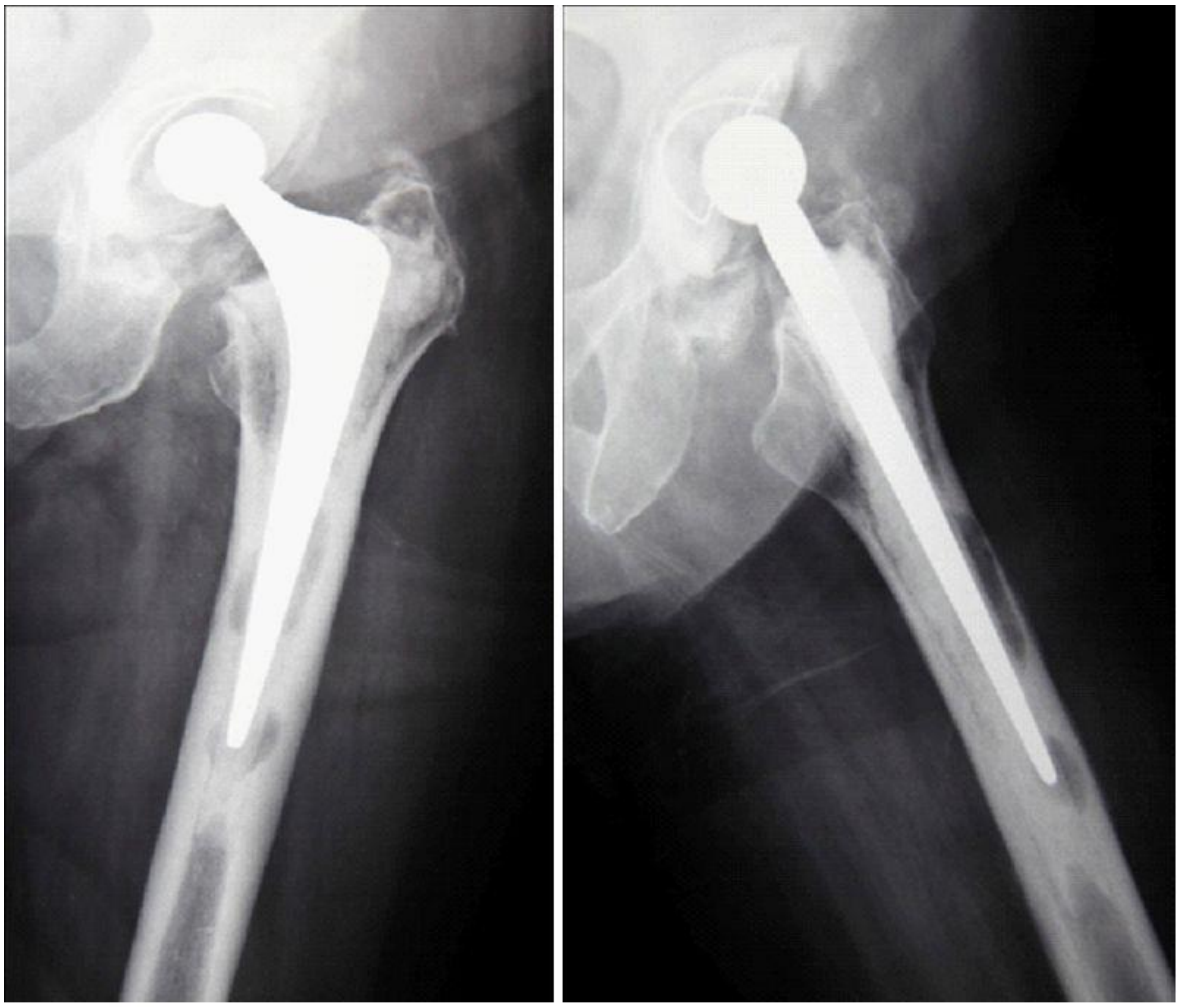

Figure 8 shows an x-ray with focal osteolysis around the prosthesis, which may be a sign of PJI.

Source: Peri-Prosthetic Joint Infection: Prevention, Diagnosis and Management (65)

Computed tomography (CT) and magnetic resonance imaging (MRI) are other possible imaging methods. CT presents a high-resolution portrait of the bone and prosthesis. On the contrary, MRI is useful to portrait soft tissue contrasts and infection signs (21, 56).

Bone scintigraphy with 99m Tc or In 111 has a very high sensitivity. The specificity however, is low (21, 56, 58).

Diagnostic imaging is useful but not absolutely necessary to diagnose PJI, since there exists conflicting evidence concerning the role of diagnostic imaging (58, 64).

1.5.6 Sonication

Sonication is a process, where bacteria and biofilm are detached from an explanted prosthesis due to usage of ultrasound waves. This results to increased sensitivity and specificity. Sensitivity of cultures in synovial fluids may be increased by sonication from 54%-55% to 79%-90% (56, 66). The cut-off point is the growth of 50 or more colonies. Thus, the presence of 50 colonies or more in synovial fluid which was prior sonicated, indicates an infection (56).

1.5.7 Conclusion

Even though there are multiple possibilities which may aid diagnosing a PJI, there is no undisputed algorithm established yet. Different criteria, like the one of Parvizi et al, can be used (57). Variety of clinical symptoms and unclear elevation of systemic biomarkers complicate the diagnose (58). According to the American Academy of Orthopaedic Surgeons, multiple test should be performed, however not all of the prior mentioned test are needed (64).

Another important factor is the time between surgery and the appearance of symptoms since the time determines the classification between acute and chronic infection. An acute infection can be treated without the need to replace the whole prosthesis. In chronic infections, it is supposed that the biofilm is already completely built. Therefore, an exchange of the whole prosthesis is usually necessary (5).

2 Materials and Methods

2.1 Patient Recruitment

The data, which was collected originated from patients, who underwent arthroplasty at the Department of Orthopaedics and Traumatology, Medical University of Graz in the space of time from June to August 2021. Every patient, who received THA, TKA, partial hip arthroplasty or unicompartmental knee arthroplasty was included. All the necessary documents were accessed via MEDocs, which is the medical information system used by all hospitals of the KAGES.

Recruited patients were followed for 3 months. This follow-up time was chosen due to the fact, that a PJI is treated differently when infection occurs later than 3 months after surgical intervention. If an arthroplasty was performed in the previously mentioned period of June to August, the date of operation was the starting point of the follow up period.

During the follow-up, all the documents of the facilities belonging to the KAGES were accessed. Facilities included were LKH Hochsteiermark, LKH Feldbach-Fürstenfeld, LKH Graz II, LKH Hartberg, LKH Murtal, LKH Mürzzuschlag, LKH Rottenmann-Bad Ausee, LKH Südsteiermark, LKH Weiz, LKH Weststeiermark, LPZ Bad Radkersburg, LPZ Knittelfeld, LPZ Mautern and LPZ Mürzzuschlag.

One hospital stay was defined when the patients arrived from home, nursing home or other hospitals than the KAGES to the time they were dismissed to one of the mentioned non-KAGES facilities. An end-to-end transfer between the KAGES facilities did not disrupt the hospital stay.

Main points of interest were the quantity of complications, which occurred in the follow-up period in relation to the number and duration of catheters inserted into the patient.

2.2 Inclusion and Exclusion Criteria

Main including criteria was a surgical arthroplasty in the previous mentioned timeline. Surgical arthroplasty had to include either of the following criteria:

I. Primary total replacement of hip or knee joint with an artificial prosthesis

II. Primary partial replacement of hip or knee joint with an artificial prosthesis

III. One-stage revision surgery including removing and implantation of a prosthesis in one setting

IV. Two-stage revision surgery including the removal of the prosthesis and filling up the space with cement containing antibiotics

V. Two-stage revision surgery including the implantation of a new prosthesis with previously removed prosthesis

Following exclusion criteria were defined:

I. Age below 18 years

II. Withdrawal of the patients consent

2.3 Data Collection

All collected data was risen by professional medical employees as nurses, students, and doctors. When searching for information, various documents were accessed. Documents concerning admission, operation, hospital stay, and records of further controls and therapies were reviewed. Patients included were anonymized.

Following data was collected:

Age
Sex (male/female)
Body-mass-index
Diabetes (present/not present)
Smoking history (yes/no)
Present infection at the time of operation (yes/no)
Type of intervention (THA, TKA, due head arthroplasty, unicompartmental knee arthroplasty or revision surgery of knee or hip)

Operation time (set-up time, patient related set-up time, operation time, postoperative patient related set-up and postoperative set-up)
Postoperative complications (infection of prosthesis, loosening of prosthesis, systemic infection, local complications and other complications)
Numeric-rating-scale maximum points at rest and at motion including the day after operation the max score was recorded
UTI during hospital stay
PVC, CVC, IDC, drainage or peritoneal catheter during hospital stay
2 or more catheters present at once
Duration of time 2 catheters were present simultaneously
Placement of the PVC (cubit, forearm, hand, central, another place)
2 different placements and 3+ different placements of the PVC
Duration of PVC, CVC, IDC and drain use
Number of PVC, CVC, IDC and drain exchanges
Catheter-related complications (infection/pain, occlusion, extravasation, bacteriaemia /systemic infection)
Period between the insertion of the catheter and catheter-related complication
Period between the intervention and the postoperative complication
Period between the insertion of catheter and the postoperative complication
Period between the catheter-related-complication and the postoperative complication
Haemoglobin (Hb) (g/dl)
Leukocytes (cells/µl)
C-reactive protein (CRP) (mg/l)
Erythrocyte sedimentation rate (ESR) (mm/h)
Procalcitonin (PCT) (µg/l)
Body temperature (C°)
Antibiogram

Table 1 list of collected data

2.3.1 Age

Age at the time of operation was recorded.

2.3.2 BMI

BMI was collected at admission by the nurses or at preoperative anaesthesia examination. When different values were recorded, the data of the preoperative examination was used.

2.3.3 Diabetes

At the admission, known diseases, such as diabetes, were assessed and recorded. Another document which did record a presence of diabetes was the preoperative anaesthesia examination. Presence of any kind of Diabetes was recorded.

2.3.4 Smoking History

Present or past abuse of nicotine was included. The data was gained from the preoperative anaesthesia examination or at admission. When no history of smoking was recorded, the patient was classified as 'non-smoker'. When smoking history was neither assessed at admission nor at preoperative anaesthesia examination, smoking status was defined as 'unknown'

2.3.5 Present Infection at Admission

Any kind of infection, diagnosed inside the period of 2 days prior to an operation and including the day of operation as well, was determined as a 'present infection at admission'. Documents of admission, ambulatory examination and hospital stay records were accessed to rule out an infection prior to documentation.

2.3.6 Type of Intervention

6 types of intervention were differentiated. THA, TKA, partial hip arthroplasty or unicompartmental knee arthroplasty was recorded, when a primary implantation was carried out on this joint. A new intervention due to a complication of an already implanted prosthesis, was stated as 'revision surgery of the knee' or 'revision surgery of the hip'. In case of two-stage revision surgery, on the first intervention the prosthesis is removed and cement is filled in. Later a new prosthesis is implanted.

In case of two-stage revision surgery, first and second intervention were recorded as a separate data sets. So in the process of data collection, one hospital stay could be disrupted by the second stage of revision surgery and a new set of data was thereby generated.

2.3.7 Operation Time

In MEDocs, certain cut-off points are timed. First point is the beginning of general set-up. This is followed up by the beginning of the patient-related set-up time, the moment of the first incision, the moment of the last stitch, the end of the postoperative patient-related set-up time and the end of general postoperative set-up time. Time periods inside recorded points were calculated with Excel. 5 different periods of time were recorded. First was the set-up time, followed by the patient-related set-up time, operation time, postoperative patient-related set-up and postoperative set-up time.

2.3.8 Postoperative Complications

Postoperative complications ware classified as simple complication, moderate complication and severe complication.

All documents available, which protocolled observation and examination within a 3-month period were accessed and searched for any kind of complication. Therefore, documents of all KAGES facilities available ware accessed.

A simple complication was present if no further diagnostic steps or interventions were necessary. Mostly those kinds of complications included local problems as:

persisting pain or swelling over a month time
wound dehiscence
local infection
haematoma
secrete running out of the wound
local cutaneous irritation

Table 2 list of simple complications

Other simple complications were muscle vein thrombosis, decubitus ulcer, alguria and herpes zoster infection.

Severe complications needed further diagnostic or therapeutic measurements and severe morbidity or mortality were associated.

Such complications are:

(Severe) Pneumonia
Spondylodiscitis
Sepsis
Periprosthetic joint infection
Present infectious fistula
Apoplex
Periprosthetic fracture
Fracture of the prosthetic inlay
acute Pancreatitis
acute Cholecystitis
Ketoacidosis

Table 3 list of severe complications

Moderate complications were such, which did not classify for light complications, nor for severe complications. Moderate complications were:

Erysipel
Chills
Deep vein thrombosis
Transient ischaemic attack
Fever
Infect of unknown origin
Acute Psychosis
Delirium
Postoperative renal insufficiency
local nerve lesion

Table 4 list of moderate complications

In some cases, the patient had multiple complications. If so, the most severe complication was included.

2.3.9 Numeric Rating Scale (NRS)

NRS score is used in clinical setting to gather information about subjective pain experience of the patient. Patients must project their pain on a scale ranging from 0 to 10. A score of 0 means no pain whereas 10 is most intense pain imaginable. Pain is usually evaluated twice, at rest and at motion.

Both maximum scores, at rest and at motion, were recorded, including postoperative day the score was achieved. When the maximal score was listed on various days, the last day of maximal score was used. The period in which NRS scores were registered, was limited to the length of the hospital stay during which the surgical procedure was undertaken.

2.3.10 Urinary Tract Infection

A UTI was only recorded, if it occurred inside the period of hospital stay in which the operation took place. The documentation of hospital stay was searched for the terms 'infection' and 'UTI'. If an infection was documented, a positive present UTI was assumed.

In case no infection was documented, the results of urinary examination were accessed, if available. It was counted as positive, when 2 of the following criteria were fulfilled:

- leukocyturia
- blood in urine in form of erythrocytes or haemoglobin
- bacteriuria

2.3.11 PVC, CVC, UTI and Drainage Use

These different kinds of catheters were included, when they were used during hospital stay in which the operation was carried out. Hospital stays at other facilities of the KAGES before or after the operation at the LKH Graz were also included, if there was an immediate transfer with end-to-end hospital stay.

Main document used to search for the use of catheters was the interprofessional documentation of hospital stay. In case no documentation of catheter use was carried out, operation records were accessed to identify catheters used at the time of operation.

Documents were searched using following terms: “PVC”, “Venflon”, “PV”, “peripheralVC”, “CVC”, “Cava”, “Port”, “IDC”, “drain”, “Redon” and “Belovac”.

Catheters had to be present before or after operation. A catheter which was placed and removed during operation was not included, since an exposition to pathogens is less likely in a hygienic environment as an operating room.

CVC were positive when catheterization via the subclavian, femoral, jugular or brachial vein was present. Tip of the catheter was hereby pushed inside the upper or lower vena cava.

2.3.12 Presence and Duration of 2 or more Catheters

Main criteria was the presence of 2 catheters or more of any kind, including multiple PVC use. For the criteria to be met, there had to be at least 2 catheters present at some point during hospital stay. However, the criteria were not met during the operation, since multiple catheterization was considered as unproblematic due do the high hygienic standards in operation rooms.

Multiple catheterization was only recorded, if there was certain evidence for 2 or more catheters being used. If there was no clear documentation of multiple catheters present at a certain point of time, a single catheterization was assumed.

2.3.13 Placement of Catheters

5 different locations of PVC placement were assessed. Those were the hand, forearm, cubita, central location and other location.

For PVC placement at the hand, mainly the backside was used. The transition of forearm to cubita is not exactly defined most of the times. Therefore, clear separation between forearm and cubita was not always possible. Centrally placed catheters were mainly CVC. ‘Different locations’ included all locations which did not meet the previously mentioned placements, including peripheral insertion of a PVC on the legs, upper arm or torso.

In case multiple placements were used, it was also documented. There was a differentiation between ‘two’ and ‘three or more’ different locations of placement.

IDC were assumed to be placed transurethral when nothing else implicated otherwise.

2.3.14 Duration of Catheters

Durations of general catheter usage was also taken from the interprofessional documentation of hospital stay. In case the date of PVC removal was not recorded, the fever chart was searched for intravenous medication applied. Duration of intravenous catheterization was then expected to be as long as the intravenous medication lasted. This also applied to the cases, in which primary insertion of a PVC was not recorded. If no intravenous medication was submitted and the day of removal was also not recorded, the day of discharge was regarded as last day of PVC use.

2.3.15 Number of Changes of Catheters

An exchange of a catheter was recorded, if one catheter was removed and a new one was inserted. In case one of multiple catheters is removed, but no new catheter was inserted, it was not accounted as an exchange.

2.3.16 Catheter-related Complication

In search for catheter-related complications, the interprofessional documentation protocol was searched for the terms “infection”, “signs of infection” and “pain”. 4 different types of complications were assessed. Infection and pain, occlusion, extravasation and bacteraemia or fungaemia.

Infection was assumed, when swelling, redness or pain was present around the insertion site. Occlusion of catheter meant that no admission of medication was possible by the catheter due to mechanical obstruction. Increased swelling during application of fluids indicated extravasation. Bacterial or fungal colonization of the catheter or BSI inside the period of catheter use was also counted as a catheter-related complication.

2.3.17 Timeline of Complication Occurrence

In case of a complication, the time of occurrence was captured in relation to other moments which relate to usage of catheters or operation.

4 different periods were listed which recorded the times between “first catheter insertion” and “catheter-related infection”, “surgical intervention” and “postoperative complication”, “first catheter insertion” and “postoperative complication” and “catheter-related complication” and “postoperative complication”.

Day of diagnosis was used as the occurrence date of a complication. Interprofessional documentation, discharge documentation and further ambulatory control examinations at the LKH Graz and at other medical facilities of the KAGES were therefore accessed.

2.3.18 Laboratory Parameters

As laboratory parameters haemoglobin, leucocyte count, CRP, ESR and procalcitonin were included. Each parameter was gathered for up to 3 months after operation. If present, the last preoperative parameter was recorded as well. Preoperative parameters, however, had to be taken inside 2 days prior to the operation.

Sometimes, a parameter was ordered multiple times a day. In this case, the parameter which was obtained during the morning routine blood removal was used. So there always is a steady time frame between the parameters.

In some cases, incorrect procedure of blood removal resulted in false results. Thus, another punctuation was needed. Only the data of the properly obtained blood samples were included.

2.3.19 Haemoglobin

Haemoglobin (Hb) is present in erythrocytes and is responsible for binding oxygen. In case of an anaemia, haemoglobin concentration is reduced. This can be induced due to a reduced production, increased depletion or loss of erythrocytes into non-vascular departments (67).

Hb is measured as g/dl. Normal Hb range differs between male and female gender. Females usually have a Hb of 12 to 16 g/dl while in males, the haemoglobin is usually between 13 and 17,5 g/dl (68). In 1958 the WHO suggested the lower limit for normal haemoglobin to be at 11 for pregnant females, 12 for non-pregnant females and 13 for males (69). Since then there have been multiple studies re-evaluating the lower limit of Hb, many of which suggested other lower limits for Hb. For some authors it also seems reasonable to define further cut-off points depending on race and age of the patient (70).

2.3.20 Leucocytes

Leucocytes are a major part of the immune system. Leucocytes include different types of cells which all play a part in the immune response. Monocytes, granulocytes, macrophage, lymphocytes and dendritic cells are all considered as leucocytes (71).

Normal leucocyte count is ranged from 3800 cells/µl to 10500 cells/µl. An increased amount of leucocytes is referred to as leucocytosis. This could be an indication for infection or inflammation. However other reasons such as leukaemia, drugs, stress and pregnancy can also result in high leucocyte cell count (72, 73). A very high white blood cell count (WBC) (>50 × 109/L) could also indicate a malignant process (72). Decreased leucocytes could indicate autoimmune disorders, virus infection, bone marrow diseases, cancer or drugs (73).

2.3.21 C-reactive Protein

In case of infection or inflammation, certain inflammation mediators are produced. These inflammation mediators then stimulate the liver, which then releases acute phase proteins, for example C-reactive protein (CRP). CRP adheres to pathogens inside the body and thereby increase the efficiency of the immune response (74). In a clinical setting, it is used an unspecific marker mainly for inflammation. It is very sensitive for bacterial infection, not so for viral infection. However, CRP can also be increased after operation or due to cancer (75).

CRP is measured in mg/L or mg/dl. Upper limit for CRP is 0,5 mg/dl. CRP has a short half-value period of 13-16 hours (74). Therefore, if an infection is present, the CRP level raises shortly after. After infection, the CRP level decreases inside 1 to 2 weeks (75).

2.3.22 Erythrocyte Sedimentation Rate

The erythrocyte sedimentation rate is a diagnostic method which may indicate the presence of infection, inflammation, autoimmune disorders, other immunological disorder or cancer. Hereby the time to sedimentation of erythrocytes in the blood serum is measured. A prolonged time to sedimentation indicates a present disorder. In pregnancy or during menstruation, the ESR can also be elevated (75).

When blood is filled in a test tube and left standing vertically, the cells of the blood sink to the bottom due to gravity. Especially the red blood cells are here important since they make up most of the cellular fraction (76). After 1 and after 2 hours the length, measured in millimetres, of clear fluid at the top of the tube is measured and expressed as mm/h (75). Most important is the descended distance after 1 hour. The distance recorded at the 2 hours mark, provides no further clinical information (75, 76). Normal speed of sedimentation is 15 mm/h or less for men and 20 mm/h or less for women. At age over 50 years, the upper limit for men and women raises about 5 mm/h (75). A sedimentation rate of over 100 mm/h has a positive predictive value for an identifiable cause of approximately 90%. Therefore, in such cases, further examinations should be considered to isolate the cause for the elevated ESR (77).

2.3.23 Procalcitonin

Procalcitonin is a pre-stage form of the thyroid hormone calcitonin. Procalcitonin is normally present in low dosage inside the blood. In case of bacterial airway infection or bloodstream infection, the level raises. The amount of procalcitonin in blood correlates with the severity of infection (75). procalcitonin has a high laboratory value for diagnosing bacterial bloodstream infection and for assessing the dynamics of such (78). Very high procalcitonin certainly indicates a bloodstream infection. In case of high procalcitonin a bacterial infection is likely (more than 2 µg/l). Moderately elevated procalcitonin alone is not conclusive. In case the procalcitonin values less than 0,5 µg/l, an infection is unlikely (75, 78).

In different studies, the cut-off point for procalcitonin varies. However, the results in mortality and morbidity were similar in relation to the procalcitonin levels. Higher procalcitonin levels are connected to higher morbidity and mortality (79).

In a big multi-national, prospective, observational study from Sager et al. in 2007 with approximately 7000 patients which tried to predict the outcome of patients with increased procalcitonin, different cut-off points were used. Cut of points of 0,05, 0,1, 0,25 and 0,5 ng/ml were used resulting in stepwise increased mortality of 1%, 3%, 7%, 13% and 15% respectively (80). A cut-off point of 0,5 ng/ml is used at KAGES facilities.

In case of infection, procalcitonin level raises inside 2-3 h. The half-period value is 24 h (75).

2.3.24 Temperature

Temperature data was obtained from fever curves. In some cases, the temperature was measured multiple times a day. In this case, the highest temperature was documented, since the occurrence of fever was focus of interest. Beginning with the date of operation, all days of the 3 month follow-up were searched for temperature measurements.

2.3.25 Antibiogram

All patients were searched for ordered antibiograms. If an antibiogram was ordered, only samples of the wound site, operation tissue, prosthesis, infected catheter or blood were accepted as fitting for this study. Bacterial colonization of skin or nasal cavity were only considered as relevant, if an infection of the prosthesis, the catheter or surgical site was diagnosed at the time. Other positive bacterial cultures taken anywhere else than previously mentioned areas, were not included in the data.

If an antibiogram was performed but no growth was detected, the antibiogram was classified as ‘no growth detected’.

2.4 Statistical Analysis

For the statistical analysis, IBM® *SPSS* Statistics was used. Correlations of data was analysed using Kendal Tau correlation. A p-value of <0,05 was regarded as statistically significant. Correlations were graded as weak, moderate or strong correlations depending on the r-value. A r-value of 0,1-0,29 was classified as weak correlation, 0,3-0,59 as moderate correlation and >0,6 as strong correlation. Same criterias applied to negative correlations (negative r-value).

3 Results

215 patients were included into this study. 4 of which underwent a surgical arthroplasty twice inside the follow-up time. Due to these 4 interventions, a total of 219 joint replacement surgeries were included.

Most of the patients were female (124/215, 57,67%). Mean age of all patients was 69,55 years, with the youngest being 27 and the oldest being 90 years old. In female patients, the mean age was slightly higher than in male patients (70,65 vs 68,05).

The most common surgical arthroplasty performed was the THA (91/219, 41,6%), followed by TKA (74/219, 33,8%), partial hip arthroplasty (24/219, 11%), revision surgery performed on the hip (14/219, 6,4%), unicompartmental knee arthroplasty (12/219, 5,5%) and revision surgery performed on the knee (4/219, 1,8%).

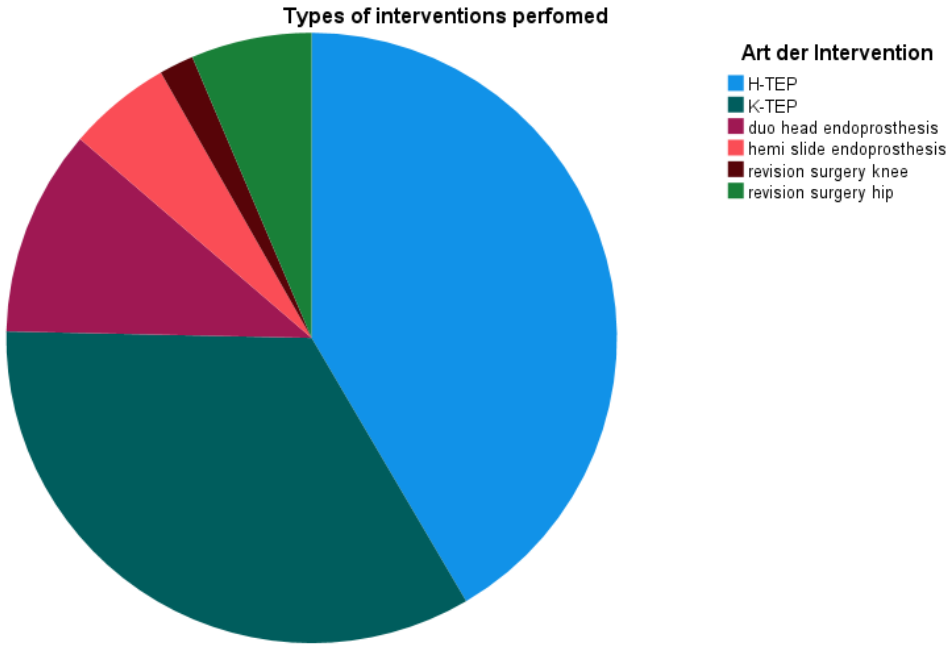

Figure 9 shows a chart pie representing the relative share of operations performed

The median time of operation was dependent on the sort of operation. A revision knee surgeries took about 112,75 minutes between the first incisions and the last suture, followed by revision hip surgeries (97,29 minutes), partial hip arthroplasty (71,04

minutes), THA (68,37 minutes), TKA (49,51 minutes) and unicompartmental knee arthroplasty (40,42 minutes).

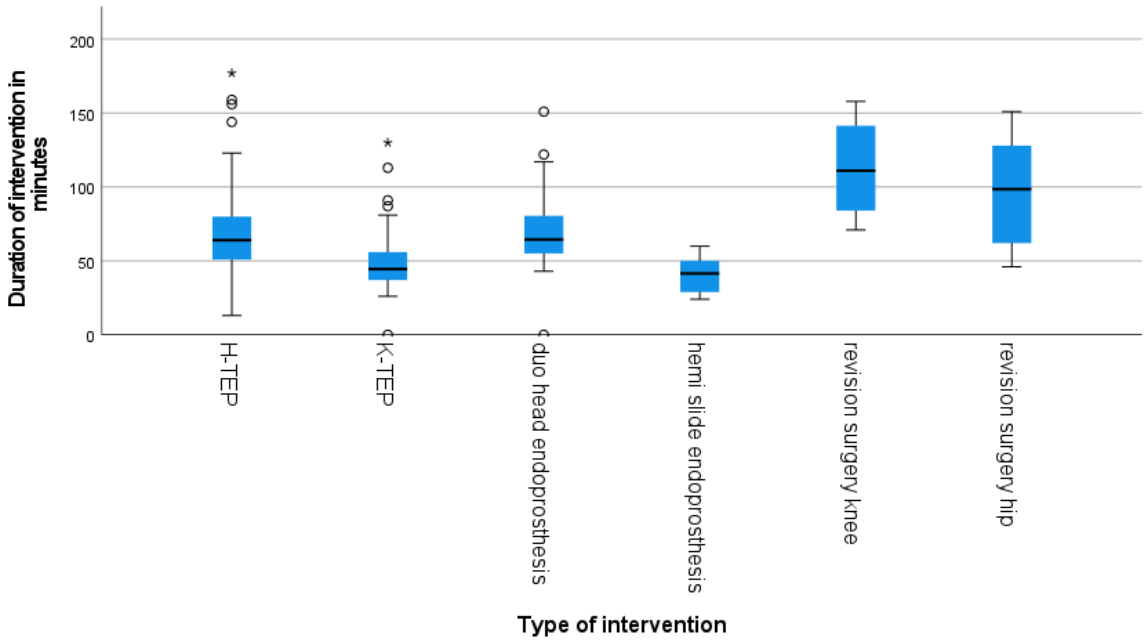

Figure 10 Boxplot comparing the duration of incision to final suture for each intervention.

During hospital stay 99,5% (218/219) of all patients had an PVC inserted at some point. 1 Person did not require a PVC. An IDC was used on 69,9% (153/219) of all patients, a drainage on 17,4% (38/219) and a CVC on 5,5% (12/219). Most of the times, multiple catheterization was present (80,8%, 177/219). Median time of multiple catheterization was 2,9 days, with a maximum time of 55 days. PVC were most frequently applied at the back of the hand (70,6%, 154/218). Cubita (43,6%, 95/218) and forearm (45,4%, 99/218) were also frequently used places for PVC. Other insertion sites were rare (0,5%). About 90 times (41,3%), 2 different insertion sites had been used. In 20 cases (9,1%), 3 or more sites were used. Mean duration time of the different catheterization types were 10,27 days for CVC, 5,46 days for PVC, 4,76 days for drainage and 3,4 days for IDC. This, however,

represents the overall time of catheterization during hospital stay and does not represent the usage time of one single catheter.

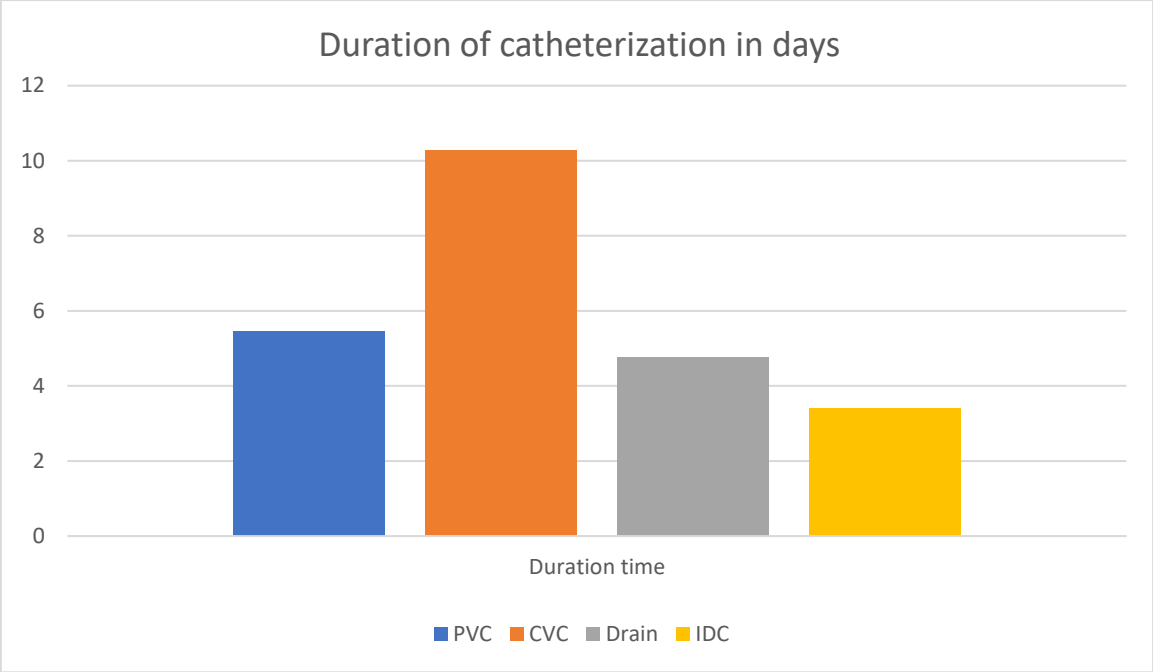

Figure 11 Bar chart comparing the median time of catheter use in days

PVC were exchanged at least once in 43,6% (95/218) of all cases. A one-time exchange was most common (29,8%, 65/218). In other patients, PVC were exchanged 2 times (9,6%, 21/218), 3 times (2,3%, 5/218), 4 times (0,9%, 2/218) and 6 times (0,9%, 2/218).

When an IDC was inserted, mostly no exchange was performed (96,1%, 147/153). 4 times a new catheter was inserted (2,6%, 4/153), a second and a third exchange was only recorded once each (0,7%, 1/153).

Usually, no exchange of CVC or drain was carried out, 91,7% (11/12) and 94,7% (36/38) respectively.

Catheter-related complications were recorded 90 times (41,1%, 90/219). Most common complications were paravasation (63,3%, 57/90) and occlusion (43,3%, 39/90). Infection (16,7%, 15/90) and systemic infection (1,1%, 1/90) were less common. When adding up all days a PVC was inserted in a patient, it sums up to a total of 1196 PVC usage days. Thus, our study resulted in 75 catheter-related complications / 1000 PVC days.

In most cases, no complication was recorded inside the 3-month follow-up period. 69 times (31,5%), a complication was recorded. Complications appear far more often in revision

surgeries of knee (75%, 3/4), revision surgeries of hip (57,1%, 8/14) and unicompartmental knee arthroplasty (58,3%, 7/12). Interventions including TKA (29,7%, 22/74), partial hip arthroplasty (29,2%, 7/24) and THA (25,3%, 23/91) produced fewer complications.

Most complications were light complications (52,2%, 36/69), followed by severe complications (26,1%, 18/69) and moderate complications (21,7%, 15/69). 2 cases of severe complications were PJI. When separating the complications depending on the type of operation, the hemi slide arthroplasty shows the highest relative share of severe complications (11,1%, 2/18).

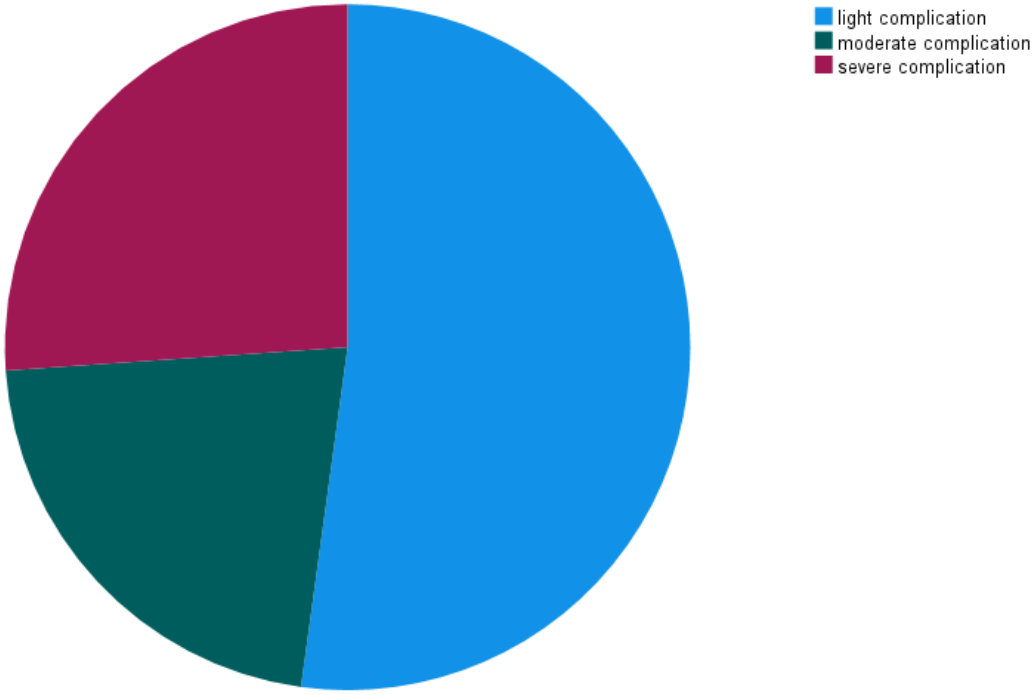

Figure 12 Pie chart showing the share of light, moderate and severe complications when present.

A bacterial culture was ordered 36 times (16,4%). 63,9% (23/36) there was no growth detected. If growth was present, the most common verified pathogen was the *staphylococcus epidermidis* (23,1%, 3/13). *Staphylococcus aureus*, *Klebsiella*, *Stayphlococcus hominis* were recorded 2 times (15,4%) each. *Germella morbillorum*, *Streptococcus mutans*, *Enterococcus faecalis* and *Serratia marscencens* were present once each (7,7%). 2 times (15,4%) other pathogens were recorded.

Using Kendal Tau-b, only the number of PVC exchanges showed a significant, weak correlation to an increased number and increased severity of complications (p=0,031, r=0,133).

Solely looking at catheter-related complications, the increased use of PVC is associated with an increase of such complications. The duration of catheter use (p=0,011, r=0,15), the use of multiple catheters at once (p=0,029, r=0,148) and the duration of multiple catheter use (p=0,041, r=0,12) all showed a significant, weak correlation to catheter-related complications. Only the number of PVC exchanges showed a significant, moderate correlation with an increased catheter-associated complication rate (p=0, r=0,522). Another factor with a significant and weak correlation to increased catheter-related complication is the number of IDC exchanges (p=0,033, r=0,144).

An increased catheter use also correlates with Leucocytes and CRP value at certain times. Duration of PVC use shows a significant and weak correlation with Leucocyte count on the 5th postoperative day (p=0,044, r=0,123), the CRP level on the 1st postoperative day (p=0,003, r=0,152) and 5th postoperative day (p=0,019, r=0,141). Also, a prolonged IDC use correlates with Leucocyte count on the 5th postoperative day (p=0,025, r=0,169), CRP level on the 3rd postoperative day (p=0,004, r=0,191) and 5th postoperative day (p=0,002, r=0,231).

An increased preoperative CRP level shows a significant and strong correlation with postoperative complications (p=0,023, r=0,701).

An increased use of PVC shows a weak correlation with antibiogram use (p=0,029, r=0,342).

Increased exchange of PVC correlates weakly with an increased pain experience during hospital stay, reflecting in a higher score on the numeric rating scale at rest (p=0,003, r =0,17) and at motion (p=0,001, r =,188). Same goes with the number of catheter-related complications and NRS at rest (p=0, r =0,234) and at motion (p=0,003, r =0,179).

A prolonged persistence of the maximal NRS score at rest correlates weakly with the duration of PVC use (p=0, r=0,2), duration of multiple catheterization (p=0,002, r=0,158) and correlates moderately with the duration of drain use (p=0,014, r=0,316).

Similar results can be seen when looking at a prolonged persistence of maximal NRS at motion. A weak correlation can be shown with increased PVC use (p=0, r=0,203), increased duration of multiple catheterization (p=0, r=0,25) and a moderate correlation to the duration of drain use (p=0,005, r=0,358).

Solely the correlations of data with a significance and possible clinical relevance have been stated above. Not all correlations have been included.

4 Discussion

The aim of this study was to analyse a potential connection of increased catheter use and an increased rate of postoperative complications, particularly an increased rate of PJI in patients which underwent an arthroplasty on hip or knee. During this study, no strong correlations were revealed between the increased catheter use and complication rate. Secondary aim was to determine, if an increased use of PVC could relate with other adverse effects as increased pain perception, increased infection parameters or catheter-related complications.

2 definitive cases of PJI were recorded in course of this study, which makes up 0,9% of all cases. This values below the complication rates found in literature (21).

4.1 Risk Factors for PJI

Several risk factors for prosthetic infection have been identified. Obesity is probably the greatest risk factor. A BMI >35 is an independent risk factor determined in multiple studies (60, 81, 82).

Other risk factors with less strong evidence are male gender, malnutrition, alcohol abuse, nicotine abuse, diabetes, presence of a drain, urinary tract infection, rheumatoid arthritis and prolonged surgery duration. With a prolonged operation time of 15 minutes, an additional increased risk of infection of 9% is expected (60, 82, 83).

Another important risk factor is the host microbiome. Long et al assumes that most surgical site infections, may be endogenous. Factors may perturb the microbiome of the host, resulting in a change of the microbe's state from 'colonization' to 'infection'. According to Long et al., 'Endogenous infection' may even be the predominant model of surgical site infection (1).

Perioperative antibiotic therapy is recommended as prevention for PJI. It is essential, that a high drug dose is used over a sufficient period. Intravenous antibiotics are administered shortly before the operation. In case of prolonged surgery time (>3h), it is recommended to administer antibiotics during the surgery as well (3). Prolonged administration of antibiotics (>48h) do not prevent surgical site infections, but do predispose to antimicrobial resistance when infection occurs (1).

The use of antibiotic cement is discussed, as the effect is not clearly proven and a promotion of bacterial resistances is discussed (21). To prevent infection with skin germs, adequate disinfection should be carried out. Preoperative screening for staphylococcus aureus school be carried out and an antimicrobial nasal gel applied in case of *staphylococcus aureus* colonization. For dental procedures with the risk of bacteraemia, antibiotic prophylaxis should be given (1, 3). Using sterile instruments, minimising operation time and restricting traffic in the operation room also reduces risk of a postoperative surgical wound infection or a PJI (55).

4.2 Catheter as Risk Factor for Infection

Catheter-associated BSI increases morbidity and mortality in hospitalised patients. Depending on the literature, an increase in mortality due to BSI of 3% - 25% is suspected (6, 38, 84).

Consistent adherence to hygienic measures can reduce the infection rate of intravascular catheters by 70% (85). Possible risk factors for catheter infection have already been analysed in several studies. Known risk factors are a prolonged duration of catheter use, number of catheters, placement of catheter in an emergency situation, intravenous antibiotic therapy, female gender, location of catheter insertion, unhygienic conditions during placement, missing regular inspection of the insertion site and missing regular verification of the indication (29, 31, 86, 87).

As prophylaxis for catheter-associated infection, a regular change of a PVC every 72-96 hours is recommended to prevent an infection (88). Benefits have been shown by several studies, which identified length of stay of a PVC as an independent risk factor for catheter-associated infections (86, 87, 89). In contrast to these findings, recent studies have found no significant difference between a routine switch and a clinically indicated switch. A clinically indicated switch has also shown to make more sense economically (90, 91). However, according to the Robert-Koch-Institution (RKI), the studies in favour of the clinical switch are not statistically significant enough (92).

The RKI has drawn up the KRINKO guidelines for infection prevention. Those guidelines include using PVC instead of CVC if possible, daily inspection of insertion site and review

of the indication, quick exchange of the catheter in case of primary insertion in an emergency setting and immediate removal of catheter in case of infection (92).

As recommended in den KRINKO criteria, a PVC should be checked daily, if an indication is present (92). However, in many cases, this daily survey is not performed. An Australian study by Alexandrou et al reviewed the daily assessment of PVC insertion site. The results stated that over one third of the PVCs (36%) used, were not assessed daily (93).

When an IDC is in place, the risk factors for UTI or BSI are like those for BSI due to use of intravascular catheters. Likewise, the duration of catheter placement is the most important factor as well. The probability of infection increases by 3% - 7% per day of use. With long-term catheterisation, the probability of infection is estimated to be at almost 100% (94). Furthermore, there seems to be a higher risk for UTI for non-ICU patients. On ICU a rate of 0,93 UTI/1000 days is assumed. In non-ICU departments, the infection rate is significantly higher (3,79 UTI/1000 days) (16).

Here again, important aspects of the KRINKO criteria are listed, which should be applied to reduce risk of UTI due to IDC use. Indications for IDC should be reviewed strictly, an IDC should be removed as soon as possible, solely incontinence is not an indication, sterile work is important for prevention, regular training on IDC insertion should be carried out and a routine change is not recommended (16).

4.3 Parenteral versus Enteral Medication

Drugs can be administered by enteral or parenteral route. Enteral administration includes oral, buccal or sublingual and rectal administration. Parenteral drugs can be administered by intravenous, intramuscular or subcutaneous injection (95).

Oral application is cost efficient, safe and convenient. Therefore it is also the most used kind of application (96). It is indicated when patients are still able to swallow and ingest the oral medication. Another benefit of oral medication is, that special forms of oral medication release their substance delayed or over a prolonged period of time (95). Oral drugs are usually absorbed in the duodenum. On the way to the duodenum the drugs must resist the gastric acid and other proteolytic enzymes, so they are not disintegrated (97).

When drugs are administered orally, it is important to be aware of the first pass effect. This refers to the effect happening when the released substance first reaches the liver. Before passing into the systemic circulation, the liver metabolises some of the substance instantly (95). Buccal and sublingual medications are absorbed by the oral mucosa. Thereby, the first pass effect is skipped, resulting in a fast onset of action. Though not all drugs can be administered by the sublingual or buccal route (98). General advantages of oral application over intravenous application are a lower risk for infection and thrombophlebitis, economic efficacy, reduction of hidden costs (such as syringes, nursing time etc.) and a reduced hospital stay for the patient (99).

When parenteral application is used, this first pass effect is avoided. The most used form of parenteral application, is the intravenous application of drugs via PVC or CVC (95). Advantages of intravenous over oral drug application is a rapid onset of effect and a precise systemic medication level, which thereby can be adjusted (96). Even though intravenous application has an earlier onset than oral application, the real impact on time in daily routine almost remains unaltered, since the time of preparation remains a huge part. Preparation includes every action necessary from the moment medication is indicated to the administration. Intravenous application includes more preparation than oral application. Therefore, the time saved using parenteral medication in contrast to oral medication is not as great as one might expect in daily routine (100).

Other indications are unstable drugs or poor absorption by the patient (95). Bioavailability is often regarded as a valid reason for prolonged intravenous drug application. However, oral drugs show no disadvantages in bioavailability when compared to intravenous therapy (99).

Summarizing the effects of oral therapy, various benefits can be determined. Patients are more satisfied with oral medication and have decreased risk for catheter-associated complications. As stated previously, oral medication also decreases costs for the health system and reduces effort for healthcare professionals. Another important factor is the compliance. It is more likely that the patient takes his medication correctly at home after hospital stay if the patient is already used to oral medication. Furthermore, it is possible to evaluate the outcome of the intravenous to oral medication conversion (100).

4.4 Intravenous to Oral Therapy Conversion

A switch from intravenous therapy to oral therapy inside 2-3 days, seems to have a benefit on the patient. An augmented use of intravenous drugs, even though no contraindications for oral therapy are present, is one of main reasons for irrational medication worldwide according to the WHO (99).

In our study, mean duration of PVC use was 5,46 days.

In literature, a shorter duration of intravenous antibiotics administration of 2-3 days followed by oral drug administration has been shown to be beneficial for the patient's outcome (1, 99, 101). It however depends on the indication since some type of infections need a prolonged antibiotic therapy.

Generally, a switch from intravenous to oral drug administration is not realised a lot of the times, even though most patients are eligible for such. It was shown by Cyriac et al, that only in one third of the cases, in which patients were eligible for a conversion from intravenous to oral therapy, a conversion was realised at day 3 of therapy (99).

Most medication is suitable for oral application. Different guidelines exist, concerning the conversion from parenteral to oral therapy. Cyriac et al recommended implementing such guidelines at hospitals and adjusting a clinical pharmacist to supervise the switch from intravenous to oral therapy (99).

A possibility to increase intravenous to oral conversion rates, is an electronic reminding system. Different studies evaluated a computerized reminder to reduce the length of PVC use. Those computerized reminders did not only warn of further intravenous therapy, but also proposed an oral alternative (102, 103). Both studies showed an increased use of oral therapy instead of parenteral therapy. The number of drugs applied intravenously was reduced by 11,1%-55%, depending on the study (102, 103). When a prompt was generated, it resulted in a switch to oral therapy or cancelation of the order in 35,6% of the cases (103).

A switch from intravenous to oral therapy contains numerous benefits, including a better cost-effectiveness, reduction in length of hospital stay, prevention of drug shortage and prevention of catheter-related complications as thrombophlebitis or sepsis (104, 105).

4.5 Oral versus Parenteral Analgesia

According to our data, the use of PVC also has a consequence on the patients' perception of pain.

In 2018, Van Loon et al analysed factors which may be associated with catheter related. Those factors were sex, American Society of Anaesthesiology classification, a patient's risk profile on the A-DIVA scale, site of cannulation on the extremity and failed insertions of PVC. However, our data did not match with the finding of van Loon et al, since duration of PVC usage and multiple insertion of PVC were not determined as a possible source for intensified pain experience (30).

When treating postoperative pain, an intravenous to oral therapy conversion seems reasonable, due to safety, effectiveness and efficacy of oral drug administration (106). Sun et al compared the pain management after joint replacement surgeries using acetaminophen. Results showed that there is no significant benefit in pain control or opioid consumption when intravenous administration is used over oral administration (107). Sufficient oral analgesia in patients with strong pain experience and no intravenous access can be provided by sublingual sufentanil for example (108). Furyk et al analysed the difference in effectiveness when Paracetamol was administered intravenously or orally. As in the study by Sun et al, no significant benefit was found using intravenous administration over oral administration (109). Wirz et al even resulted in better pain control using oral administration. Therefore, intravenous patient-controlled analgesia (PCA) was compared with oral PCA. Results showed, that an oral PCA provided better pain control, which was measured with NRS score at rest and at motion and the requested number of boluses by the patient (110).

In general, postoperative pain relief is very important to restore function after joint replacement surgery (111). Analgetic administration often remains intravenous. According to the previously mentioned criteria of the RKI, a daily review of the indication should be carried out (92). This raises the question if a relevant indication is always present, or the measures are not carried out properly.

5 Limitations

There are some limitations to be found in our study. First of all, the number of recorded cases is limited. Those 219 joint replacement surgeries recorded are not enough to verify a correlation between increased catheter use and PJI or other complications. Especially, findings concerning PJI cannot be verified since only 2 PJI have been recorded in our study. Furthermore, the follow up period of 3 months should be extended so possible correlations can be revealed.

A confounding factor could be the inclusion of revision surgeries, since these surgeries have a higher overall risk of infection (21).

Another confounding factor might apply to the correlation of PVC exchanges and catheter-related complications, since an occurrence of a catheter-related complication mostly results in removal of the PVC. However, if intravenous administration of drugs remains necessary, another PVC must be inserted. Thus, a higher exchange number of PVC does not necessarily mean an increased risk for catheter-related complication, since in many cases the occurrence of a catheter-related complication results in an exchange of the catheter. So, the relation of those 2 factors can cofound the results found.

Most literature, which we found referring to duration of intravenous application of medication concerned the use of antibiotics particularly. Since in our study there was no separation concerning the medication used, the results reported in literature do only apply partially.

Our study does not include the duration of each catheter used, since we only recorded the overall time, a catheter was used during hospital stay. Thus, future studies should record the duration of each catheter usage and assess the effect on the risk of infection.

6 Conclusion

Literature proposes, that a conversion of intravenous to oral drugs is mainly possible and also reasonable (99). Oral drug administration results in less adverse effects and in better cost effectiveness (106). Studies have also shown that there is no disadvantage in pain control when using oral analgesia (107-110). When using antibiotics, an early conversion around day 3 also has been shown to be beneficial for the patient (99). A possibility to decrease the length of intravenous therapy might be a computerized reminding system which results in higher conversion rates, according to multiple studies (102, 103). Another study proposed implementing regular trainings and guidelines for indication, documentation and care, so the number of infections can be reduced (31).

However, to validate a correlation between increased catheter use and increased complications, a higher number of cases would be needed. Also, an adaption of the including and excluding criteria would be needed, so confounding factors can be further eliminated.

References

1. Long DR, Alverdy JC, Vavilala MS. Emerging Paradigms in the Prevention of Surgical Site Infection: The Patient Microbiome and Antimicrobial Resistance. Anesthesiology. 2022;137(2):252-62.
2. Austria S. Medizinische Leistungen 2021 [Available from: https://pic.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/stationaere_aufenthalte/medizinische_leistungen/index.html.
3. Preininger B, Trampuz A. Die Behandlung periprothetischer Infektionen 2017 [Available from: https://www.universimed.com/ch/article/orthopaedie-traumatologie/die-behandlung-periprothetischer-infektionen-2098399.
4. Legout L, Senneville E. Periprosthetic joint infections: clinical and bench research. ScientificWorldJournal. 2013;2013:549091.
5. Otto-Lambertz C, Yagdiran A, Wallscheid F, Eysel P, Jung N. Periprosthetic Infection in Joint Replacement. Dtsch Arztebl Int. 2017;114(20):347-53.
6. Thalhammer F, Gustorff B, Allerberger F, Bellmann R, Fruhwald S. Gefäßkatheter-bezogene Infektionen. Österreichische Ärztezeitung. 2011 April:1-12.
7. (DGOOC) DGfOuOC. Prävention und Therapie der Gonarthrose. AWMF Leitlinien. 2018.
8. school HHPHm. Joint Replacement n. d. [Available from: https://www.health.harvard.edu/topics/joint-replacement.
9. Lützner Jörg, Schmitt Jochen. Knietotalendoprothese: Wann ist der Ersatz angebracht? : deutsches Ärzteblatt; 2016 [Available from: https://www.aerzteblatt.de/archiv/183359/Knietotalendoprothese-Wann-ist-der-Ersatz-angebracht.
10. Amboss. Operative Verfahren der Unfallchirurgie/Orthopädie 2021 [Available from: https://next.amboss.com/de/article/vl0AAT?q=prothesenlockerung#Z2ef56aadcdb89e41fed9c2970d5c352f.
11. Information NCfB. Catheters 2011 [Available from: https://www.ncbi.nlm.nih.gov/mesh/68057785.
12. Amboss. Anlage eines peripheren Venenverweilkatheters 2021 [Available from: https://next.amboss.com/de/article/sn0tug?q=peripherven%C3%B6ser%20katheter#Zd2ef81902548c3b7ba2422fc7ddf24e8.
13. Tse A, Schick MA. Central Line Placement. StatPearls. Treasure Island (FL)2021.
14. Amboss. Flüssigkeits- und Volumentherapie 2021 [Available from: https://next.amboss.com/de/article/fM0kLg?q=zentralven%C3%B6ser%20katheter#Zf94720195e1e3b09ffcabe078358680c.
15. Amboss. Anlage eines Blasenkatheters 2021 [Available from: https://next.amboss.com/de/article/vJ0ADS?q=blasenkathter#Z57f05fda4fddaf539dd5fdebeacbe6d9.
16. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz. Prävention und Kontrolle Katheter-assoziierter Harnwegsinfektionen. 2015;6:641-50.
17. Niedergethmann M, Bludau F, Dusch N, Nowak K, Post S. [Significance of drains in surgery]. Chirurg. 2011;82(12):1079-84.
18. Amboss. Drainagen 2021 [Available from: https://next.amboss.com/de/article/8s0O9h?q=drainage#Z9cced7e5509c9faf430ac1f8ce46ee70.
19. Long H, Li Z, Xing D, Ke Y, Lin J. The usage of drainage after primary total hip or knee arthroplasty: best evidence selection and risk of bias considerations. BMC Musculoskelet Disord. 2021;22(1):1028.

20. Ribeiro M, Monteiro FJ, Ferraz MP. Infection of orthopedic implants with emphasis on bacterial adhesion process and techniques used in studying bacterial-material interactions. Biomatter. 2012;2(4):176-94.
21. Ritschl P, Thalhammer F, al. e. Protheseninfektion in der Orthopädie. Österreichische Ärztezeitung Supplementum. 2008 Juni:1-16.
22. Pant N, Eisen DP. Non-Antimicrobial Adjuvant Strategies to Tackle Biofilm-Related Staphylococcus aureus Prosthetic Joint Infections. Antibiotics (Basel). 2021;10(9).
23. Bundesministerium für Soziales G, Pflege und Konsumentenschutz. Medizinische Leistungen bei stationären Krankenhausaufenthalten 2021 [Available from: http://www.kaz.bmg.gv.at/medizinische-dokumentation/leistungen.html.
24. Leitner L, Turk S, Heidinger M, Stockl B, Posch F, Maurer-Ertl W, et al. Trends and Economic Impact of Hip and Knee Arthroplasty in Central Europe: Findings from the Austrian National Database. Sci Rep. 2018;8(1):4707.
25. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am. 2007;89(4):780-5.
26. Linkage SMRaD. SIRIS – Swiss national registry for hip and knee replacement 2021 [Available from: https://www.swissrdl.unibe.ch/registries/siris/index_eng.html.
27. Connaughton A, Childs A, Dylewski S, Sabesan VJ. Biofilm Disrupting Technology for Orthopedic Implants: What's on the Horizon? Front Med (Lausanne). 2014;1:22.
28. Holinka J, Windhager R. [Management of prosthetic joint infections]. Orthopade. 2016;45(4):359-73; quiz 74.
29. Mermel LA. Short-term Peripheral Venous Catheter-Related Bloodstream Infections: A Systematic Review. Clin Infect Dis. 2017;65(10):1757-62.
30. van Loon FH, Puijn LA, van Aarle WH, Dierick-van Daele AT, Bouwman AR. Pain upon inserting a peripheral intravenous catheter: Size does not matter. J Vasc Access. 2018;19(3):258-65.
31. Bonsignore M, Tafelski S, Schwegmann K, Meier-Hellmann A, Witzke O, Nachtigall I. Risk Factors for Vascular Catheter Infections-Findings of a Point-Prevalence Study in 78 Hospitals. Dtsch Arztebl Int. 2021;118(29-30):503-4.
32. Gledstone-Brown L, McHugh D. Review article: Idle 'just-in-case' peripheral intravenous cannulas in the emergency department: Is something wrong? Emerg Med Australas. 2018;30(3):309-26.
33. Blanco-Mavillard I, Rodriguez-Calero MA, de Pedro-Gomez J, Parra-Garcia G, Fernandez-Fernandez I, Castro-Sanchez E. Incidence of peripheral intravenous catheter failure among inpatients: variability between microbiological data and clinical signs and symptoms. Antimicrob Resist Infect Control. 2019;8:124.
34. Marsh N, Webster J, Larson E, Cooke M, Mihala G, Rickard CM. Observational Study of Peripheral Intravenous Catheter Outcomes in Adult Hospitalized Patients: A Multivariable Analysis of Peripheral Intravenous Catheter Failure. J Hosp Med. 2018;13(2):83-9.
35. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. Mayo Clin Proc. 2006;81(9):1159-71.
36. Pujol M, Hornero A, Saballs M, Argerich MJ, Verdaguer R, Cisnal M, et al. Clinical epidemiology and outcomes of peripheral venous catheter-related bloodstream infections at a university-affiliated hospital. J Hosp Infect. 2007;67(1):22-9.
37. Kallel H, Houcke S, Resiere D, Roy M, Mayence C, Mathien C, et al. Epidemiology and Prognosis of Intensive Care Unit-Acquired Bloodstream Infection. Am J Trop Med Hyg. 2020;103(1):508-14.
38. Rosenthal VD, Bat-Erdene I, Gupta D, Belkebir S, Rajhans P, Zand F, et al. Six-year multicenter study on short-term peripheral venous catheters-related bloodstream infection rates in 727 intensive care units of 268 hospitals in 141 cities of 42 countries of Africa, the Americas, Eastern Mediterranean, Europe, South East Asia, and Western Pacific Regions: International

Nosocomial Infection Control Consortium (INICC) findings. Infect Control Hosp Epidemiol. 2020;41(5):553-63.
39. Tacconelli E, Smith G, Hieke K, Lafuma A, Bastide P. Epidemiology, medical outcomes and costs of catheter-related bloodstream infections in intensive care units of four European countries: literature- and registry-based estimates. J Hosp Infect. 2009;72(2):97-103.
40. Leistner R, Hirsemann E, Bloch A, Gastmeier P, Geffers C. Costs and prolonged length of stay of central venous catheter-associated bloodstream infections (CVC BSI): a matched prospective cohort study. Infection. 2014;42(1):31-6.
41. Gonzalez Lopez JL, Arribi Vilela A, Fernandez del Palacio E, Olivares Corral J, Benedicto Marti C, Herrera Portal P. Indwell times, complications and costs of open vs closed safety peripheral intravenous catheters: a randomized study. J Hosp Infect. 2014;86(2):117-26.
42. Chenoweth C, Saint S. Preventing catheter-associated urinary tract infections in the intensive care unit. Crit Care Clin. 2013;29(1):19-32.
43. Parker V, Giles M, Graham L, Suthers B, Watts W, O'Brien T, et al. Avoiding inappropriate urinary catheter use and catheter-associated urinary tract infection (CAUTI): a pre-post control intervention study. BMC Health Serv Res. 2017;17(1):314.
44. Tsai Y, Chang CH, Lin YC, Lee SH, Hsieh PH, Chang Y. Different microbiological profiles between hip and knee prosthetic joint infections. J Orthop Surg (Hong Kong). 2019;27(2):2309499019847768.
45. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis. 2003;36(1):53-9.
46. Ruiz-Giardin JM, Ochoa Chamorro I, Velazquez Rios L, Jaqueti Aroca J, Garcia Arata MI, SanMartin Lopez JV, et al. Blood stream infections associated with central and peripheral venous catheters. BMC Infect Dis. 2019;19(1):841.
47. Lara MO, Lucas TC, Kalapothakis E, Thomasini RL, Machado CJ. Molecular tracking of pathogens in central venous catheter. J Vasc Access. 2021;22(2):209-17.
48. Wyllie DH, Crook DW, Peto TE. Mortality after Staphylococcus aureus bacteraemia in two hospitals in Oxfordshire, 1997-2003: cohort study. BMJ. 2006;333(7562):281.
49. Freire MO, Van Dyke TE. Natural resolution of inflammation. Periodontol 2000. 2013;63(1):149-64.
50. Lee JT, Kalani MA. Treating superficial venous thrombophlebitis. J Natl Compr Canc Netw. 2008;6(8):760-5.
51. Chu CM, Lowder JL. Diagnosis and treatment of urinary tract infections across age groups. Am J Obstet Gynecol. 2018;219(1):40-51.
52. McLellan LK, Hunstad DA. Urinary Tract Infection: Pathogenesis and Outlook. Trends Mol Med. 2016;22(11):946-57.
53. Barrett L, Atkins B. The clinical presentation of prosthetic joint infection. J Antimicrob Chemother. 2014;69 Suppl 1:i25-7.
54. Okwechime B, Ayodele O, Pearce OJ. The management of prosthetic joint infection in the community: a guide for general practice. Br J Gen Pract. 2017;67(655):88-90.
55. Surgeons AAoO. Joint Replacement Infection January 2018 [Available from: https://www.orthoinfo.org/en/diseases--conditions/joint-replacement-infection/.
56. Izakovicova P, Borens O, Trampuz A. Periprosthetic joint infection: current concepts and outlook. EFORT Open Rev. 2019;4(7):482-94.
57. Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. J Arthroplasty. 2018;33(5):1309-14 e2.
58. Kim SJ, Cho YJ. Current Guideline for Diagnosis of Periprosthetic Joint Infection: A Review Article. Hip Pelvis. 2021;33(1):11-7.
59. Xie K, Dai K, Qu X, Yan M. Serum and Synovial Fluid Interleukin-6 for the Diagnosis of Periprosthetic Joint Infection. Sci Rep. 2017;7(1):1496.

60. Surgeons AAoO. American Academy of Orthopaedic Surgeons Evidence-

Based Clinical Practice Guideline for Diagnosis and Prevention of Periprosthetic Joint Infections 2019 March 11 [Available from: https://www.aaos.org/pjiguideline.
61. Greidanus NV, Masri BA, Garbuz DS, Wilson SD, McAlinden MG, Xu M, et al. Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty. A prospective evaluation. J Bone Joint Surg Am. 2007;89(7):1409-16.
62. Moser KA, Pearson LN, Pelt CE, Olson JD, Goodwin AJ, Isom JA, et al. Letter to the Editor on "The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria". J Arthroplasty. 2020;35(9):2682-3.
63. Williams JL, Norman P, Stockley I. The value of hip aspiration versus tissue biopsy in diagnosing infection before exchange hip arthroplasty surgery. J Arthroplasty. 2004;19(5):582-6.
64. Tubb CC, Polkowksi GG, Krause B. Diagnosis and Prevention of Periprosthetic Joint Infections. J Am Acad Orthop Surg. 2020;28(8):e340-e8.
65. Gheiti AJC, Mulhall KJ. Peri-Prosthetic Joint Infection: Prevention, Diagnosis and Management London2013 [Available from: https://www.intechopen.com/chapters/42848 doi: 10.5772/53247.
66. Rothenberg AC, Wilson AE, Hayes JP, O'Malley MJ, Klatt BA. Sonication of Arthroplasty Implants Improves Accuracy of Periprosthetic Joint Infection Cultures. Clin Orthop Relat Res. 2017;475(7):1827-36.
67. Österreich ÖG. Hämoglobin 2020 [Available from: https://www.gesundheit.gv.at/labor/laborwerte/blutbild/haemoglobin.
68. Herold G. Innere Medizin 2017. Köln: Gerd Herold; 2016. 31 p.
69. Organization WH. Nutritional anaemias. World Health Organ Tech Rep Ser. 1968;405:9-10.
70. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? Blood. 2006;107(5):1747-50.
71. Hans-Christian Pape, Armin Kurtz, Stefan Silbernagl. Physiologie. Stuttgart: Georg Thieme Verlag; 2018. 279 p.
72. Chabot-Richards DS, George TI. Leukocytosis. Int J Lab Hematol. 2014;36(3):279-88.
73. Internisten BdIu. Leukozyten n. d. [Available from: https://www.internisten-im-netz.de/mediathek/blutbild-erklaerung/leukozyten.html.
74. Österreich ÖG. C-reaktives Protein (CRP) 2020 [Available from: https://www.gesundheit.gv.at/labor/laborwerte/infektionen-bakterien/crp.
75. Herold G. Innere Medizin 2017. Köln: Gerd Herold; 2016. 969 p.
76. Österreich ÖG. Blutsenkungsgeschwindigkeit 2020 [Available from: https://www.gesundheit.gv.at/labor/laborwerte/infektionen-bakterien/blutsenkung.
77. Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, et al. Erythrocyte Sedimentation Rate and C-reactive Protein Measurements and Their Relevance in Clinical Medicine. WMJ. 2016;115(6):317-21.
78. Österreich ÖG. Procalcitonin 2020 [Available from: https://www.gesundheit.gv.at/labor/laborwerte/infektionen-bakterien/procalcitonin.
79. Hamade B, Huang DT. Procalcitonin: Where Are We Now? Crit Care Clin. 2020;36(1):23-40.
80. Sager R, Wirz Y, Amin D, Amin A, Hausfater P, Huber A, et al. Are admission procalcitonin levels universal mortality predictors across different medical emergency patient populations? Results from the multi-national, prospective, observational TRIAGE study. Clin Chem Lab Med. 2017;55(12):1873-80.
81. Lubbeke A, Zingg M, Vu D, Miozzari HH, Christofilopoulos P, Uckay I, et al. Body mass and weight thresholds for increased prosthetic joint infection rates after primary total joint arthroplasty. Acta Orthop. 2016;87(2):132-8.

82. Namba RS, Inacio MC, Paxton EW. Risk factors associated with deep surgical site infections after primary total knee arthroplasty: an analysis of 56,216 knees. J Bone Joint Surg Am. 2013;95(9):775-82.
83. Kong L, Cao J, Zhang Y, Ding W, Shen Y. Risk factors for periprosthetic joint infection following primary total hip or knee arthroplasty: a meta-analysis. Int Wound J. 2017;14(3):529-36.
84. Bessis S, Cassir N, Meddeb L, Remacle AB, Soussan J, Vidal V, et al. Early mortality attributable to PICC-lines in 4 public hospitals of Marseille from 2010 to 2016 (Revised V3). Medicine (Baltimore). 2020;99(1):e18494.
85. Witte F. Katheterhygiene: Jede Infektion ist eine zu viel: Deutsches Ärzteblatt; 2017 [Available from: https://www.aerzteblatt.de/archiv/195202/Katheterhygiene-Jede-Infektion-ist-eine-zu-viel.
86. Cicolini G, Manzoli L, Simonetti V, Flacco ME, Comparcini D, Capasso L, et al. Phlebitis risk varies by peripheral venous catheter site and increases after 96 hours: a large multi-centre prospective study. J Adv Nurs. 2014;70(11):2539-49.
87. Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters. A randomized controlled trial. Ann Intern Med. 1991;114(10):845-54.
88. O'Grady NP, Alexander M, Burns LA, Dellinger EP, Garland J, Heard SO, et al. Guidelines for the prevention of intravascular catheter-related infections. Clin Infect Dis. 2011;52(9):e162-93.
89. Collignon PJ. Intravascular catheter associated sepsis: a common problem. The Australian Study on Intravascular Catheter Associated Sepsis. Med J Aust. 1994;161(6):374-8.
90. Rickard CM, Webster J, Wallis MC, Marsh N, McGrail MR, French V, et al. Routine versus clinically indicated replacement of peripheral intravenous catheters: a randomised controlled equivalence trial. Lancet. 2012;380(9847):1066-74.
91. Tuffaha HW, Rickard CM, Webster J, Marsh N, Gordon L, Wallis M, et al. Cost-effectiveness analysis of clinically indicated versus routine replacement of peripheral intravenous catheters. Appl Health Econ Health Policy. 2014;12(1):51-8.
92. Gesundheitsschutz BG. Prävention von Infektionen, die von Gefäßkathetern ausgehen : Teil 2 - Periphervenöse Verweilkanülen und arterielle Katheter Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut. Springer-Verlag Berlin Heidelberg. 2017 Feb.
93. Alexandrou E, Ray-Barruel G, Carr PJ, Frost SA, Inwood S, Higgins N, et al. Use of Short Peripheral Intravenous Catheters: Characteristics, Management, and Outcomes Worldwide. J Hosp Med. 2018;13(5).
94. Flores-Mireles A, Hreha TN, Hunstad DA. Pathophysiology, Treatment, and Prevention of Catheter-Associated Urinary Tract Infection. Top Spinal Cord Inj Rehabil. 2019;25(3):228-40.
95. Kim J, De Jesus O. Medication Routes of Administration. StatPearls. Treasure Island (FL)2021.
96. Le J. Drug administration: MSD Manuals Consumer Version; 2020 [Available from: https://www.msdmanuals.com/home/drugs/administration-and-kinetics-of-drugs/drug-administration.
97. Jennifer L. Drug Absorption: MSD Manuals professional version; 2020 [Available from: https://www.msdmanuals.com/professional/clinical-pharmacology/pharmacokinetics/drug-absorption?query=Drug%20Administration#v43449621.
98. Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin Pharmacokinet. 2002;41(9):661-80.
99. Cyriac JM, James E. Switch over from intravenous to oral therapy: A concise overview. J Pharmacol Pharmacother. 2014;5(2):83-7.
100. Sandner-Kiesling A, Pichler B, Pretterhofer G. Schmerztherapie – CAVEATs. [Presentation]. Medical University of Graz. Department of Special Anesthesiology, Pain and Intensive Care Medicine
101. Shrayteh ZM, Rahal MK, Malaeb DN. Practice of switch from intravenous to oral antibiotics. Springerplus. 2014;3:717.

102. Bogucki B, Jacobs BR, Hingle J, Clinical Informatics Outcomes Research G. Computerized reminders reduce the use of medications during shortages. J Am Med Inform Assoc. 2004;11(4):278-80.
103. Fischer MA, Solomon DH, Teich JM, Avorn J. Conversion from intravenous to oral medications: assessment of a computerized intervention for hospitalized patients. Arch Intern Med. 2003;163(21):2585-9.
104. Cunha BA. Intravenous to oral antibiotic switch therapy. Drugs Today (Barc). 2001;37(5):311-9.
105. Babonji A, Darwesh B, Al-Alwai M. Implementation of pharmacist-managed early switch from intravenous to oral therapy using electronic identification at a tertiary academic hospital. Saudi Pharm J. 2021;29(4):324-36.
106. Pergolizzi JV, Jr., Raffa RB, Tallarida R, Taylor R, Labhsetwar SA. Continuous multimechanistic postoperative analgesia: a rationale for transitioning from intravenous acetaminophen and opioids to oral formulations. Pain Pract. 2012;12(2):159-73.
107. Sun L, Zhu X, Zou J, Li Y, Han W. Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: A systematic review and meta-analysis. Medicine (Baltimore). 2018;97(6):e9751.
108. Reardon CE, Kane-Gill SL, Smithburger PL, Dasta JF. Sufentanil Sublingual Tablet: A New Option for Acute Pain Management. Ann Pharmacother. 2019;53(12):1220-6.
109. Furyk J, Levas D, Close B, Laspina K, Fitzpatrick M, Robinson K, et al. Intravenous versus oral paracetamol for acute pain in adults in the emergency department setting: a prospective, double-blind, double-dummy, randomised controlled trial. Emerg Med J. 2018;35(3):179-84.
110. Wirz S, Seidensticker S, Shtrichman R. Patient-Controlled Analgesia (PCA): Intravenous Administration (IV-PCA) versus Oral Administration (Oral-PCA) by Using a Novel Device (PCoA(R) Acute) for Hospitalized Patients with Acute Postoperative Pain-A Comparative Retrospective Study. Pain Res Manag. 2021;2021:2542010.
111. van Egmond JC, Verburg H, Vehmeijer SB, Mathijssen NM. Early follow-up after primary total knee and total hip arthroplasty with rapid recovery : Focus groups. Acta Orthop Belg. 2015;81(3):447-53.