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Review

Periprosthetic Infections after Total Hip and Knee Arthroplasty – A Review

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ABSTRACT

Periprosthetic joint infections (PJI) in orthopedic surgery are considered to be very serious and dangerous complications of total joint arthroplasty. PJI becomes a long-lasting medical problem and a heavy burden on patient and his family. Patients with such a complication are a significant financial burden for the health care system. Recognizing this issue, investing in scientific research and simultaneously developing technologies in medicine are efforts taken to increase successfulness in preventing and treating PJI. Each year the number of total joint arthroplasties increases which entails a rise in the number of complications among which infections are the leading ones. Sometimes, in the worst case scenarios, infections can endanger patients' lives. New procedural algorithms and new diagnostic possibilities help us make accurate and early diagnoses of postoperative PJI with a great degree of certainty. These diagnostic methods include laboratory tests, imaging, histopathology and microbiological analyses. Treatment options depend on many factors which include the onset of symptoms, patients' general physical condition and type of pathogen. The approach to treating PJI is complex and it requires a multidisciplinary approach in order to ensure the most successful treatment possible. For adequate and successful treatment we need to take into account antibiotic therapy, one-stage or two-stage revision, Girdlestone operation, athrodesis and amputation. In this review we will try to sum up all relevant findings and suggest further steps in management of PJI.

Key words: *periprosthetic joint infection, total knee arthroplasty, total hip arthroplasty, treatment, antibiotics*

Introduction

In orthopedics, periprosthetic joint infections (PJI) are considered to be very serious and dangerous complications of total joint arthroplasty (TJA)[1]. Because of the usage of different material in orthopedics (endoprosthesis, osteosynthetic material), regardless of whether aseptic surgical principles are observed, the risk of infections is relatively high. The major cause of revision surgery after total knee arthroplasty (TKA) is infection[2]. Also, after total hip arthroplasty (THA) and the occurrence of infection of primary THA, revision surgery is the largest and the most frequent problem we can enounter[3]. PJI becomes a long-lasting medical problem and heavy burden on patient and his family. Accurate and early diagnosis of postoperative PJI is the key to success. What is most important is to differentiate between septic and aseptic loosening of TJA for further successful treatment. In 11% of cases the cause of PJI is not detected despite all diagnostic tools which confirm the existence of infection[4]. The approach to treating PJI is complex and it requires a multidisciplinary approach in order to ensure the most successful treatment possible. PJI treatment principles and techniques are numerous depending on the pathogen, patient age, general physical condition, functional requirements and bone quality. When deciding upon the treatment method, each patient should be approached individually.

Therefore, the purpose of this review is to sum up all relevant findings on PJI which pose a very important challenge that accompanies TKA and THA in orthopedics. The review will provide a critical opinion on the latest research

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results and suggest further steps that orthopedic surgeons could take in their everyday clinical work when dealing with PJI.

Epidemiology and Etiology

THA and TKA infections are mainly caused by Staphylococcus aureus and Staphylococcus epidermidis. According to available literature, S. aureus is in 55–58% of cases a detected cause of infection which makes it the leading pathogen based on frequency. Infections can also be caused by other infectious agents such as Streptococcus species and gram negative microorganisms, Klebsiella, Escherichia coli and Pseudomonas, but to a much lesser extent. In a small number of patients whose immune system is compromised, there is a possibility of infection caused by Candida albicans and Mycobacterium tuberculosis[5].

In a study which included 69,663 patients who underwent TKA surgery, 1080 patients had an infection confirmed within a two year period after TKA surgery, and 320 patients had an infection confirmed in the period from 2 to 10 years[6].

At the surface of endoprosthesis bacteria create a biofilm which gives them protection from the immune system and antibiotics. The biofilm enables the development of chronic PJI which is very difficult to treat using antibiotic therapy. Antibiotics cannot penetrate the biofilm and the bacteria keep differentiating which supports the chronic PJI[7]. Antibiotic action is focused on those bacteria which are free and separated from the biofilm. By limiting the dispersion of bacteria and their quantity, we temporarily reduce the clinical symptoms of PJI. As soon as the concentration of antibiotics decreases at the site of infection because therapy is no longer administered, clinical symptoms of infection return. This keeps occurring until the biofilm is mechanically removed from the endoprosthesis and thus the source of infection eradicated, which is carried out sugically[8].

Diagnosis

Diagnosis always starts with a detailed medical history and clinical examination which can be of crucial importance for taking further steps and choosing targeted examinations in order to make a definite diagnosis in the shortest possible time.

A patient with a TJA infection most frequently complains about pain localized in the area of an implant. Swelling, redness, and hyperthermia can appear which speak in favor of the infectious process. Pyrexia, shivering, chills, loss of mobility in the joint, and unwillingness to use the limb are signs which additionally confirm the infection although they are rarely present. Secretion of different consistency can sometimes appear in the scar area. All these symptoms can indicate a PJI, but they are unspecific.

Usually the first and the cheapest test which is done when there is suspicion of PJI is differential blood count. In this first step we want to know whether peripheral blood leukocytes, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are elevated. Leukocytes obtained from peripheral blood are often within the normal range so they are not a significant diagnostic test. Acute hematogenous infections are an exception where values can be elevated due to the presence of bacteraemia[5].

We have to be aware that CRP and ESR values can be elevated because of some other diseases or conditions what diminishes their diagnostic significance. ESR has little significance in diagnosing PJI because of its low sensitivity and specificity, as opposed to CRP which has a more significant role in making a diagnosis. CRP combined with interleukine-6 (IL-6) represents a powerful tool in diagnosing PJI. In patients with the analysis of postoperative PJI markers, the following results were obtained: CRP sensitivity 0.95 and specificity 0.96 as opposed to IL-6 which had the same sensitivity value but less specificity 0.87[9]. It has been proved that IL-6 values were also elevated in patients who had PJI in the last 6 months as opposed to patients who did not have PJI what is not the case with CRP values which were the same in both groups of patients. It has been noticed in the study that a decrease of elevated IL-6 values occurs after 6 months from receiving PJI treatment[10].

Exact tests are needed for proving PJI whose results will not leave room for doubt. Scientific community is intensively working on this and advances are obvious. The leukocyte esterase strip test, as a cheap and easy to do test, could become a significant contribution in the battle against PJI. Testing is carried out so that synovial fluid is taken after TKA and THA and put on strip test. Its great advantage is its high accuracy in diagnosing and getting results in 60–120 seconds[11].

Tissue culture is a diagnostic test which is very helpful in detecting PJI. Samples for analysis can be divided into superficial swab and intraoperative tissue culture. It is extremely important to adhere to aseptic protocols when taking samples for microbial analysis in order to avoid sample contamination. Patients need to be kept without antibiotic therapy for minimally 2 weeks before taking samples otherwise tests could show falsely negative PJI results. Superficial swab culture is useful for a faster analysis and isolating PJI infectious agents, while the results of intraoperative tissue culture are considered to be the most important data based on which the whole PJI treatment is founded on. In a research conducted on the same patients, there was overlapping between the results of superficial swab and intraoperative tissue samples in 80.3% of cases[12]. This indicates that both tests need to be carried out because each has its advantages and disadvantages.

Joint aspiration should be obligatory in patients with THA and TKA if inflammation markers are elevated or in case there is a need for revision surgery. Trampuz et al. conducted a research on synovial fluid in patients with TKA where he defined the values for diagnosing PJI after

joint aspiration was performed. It was concluded in the research that the number of leukocytes above 1700/μL and neutrophil values above 65% in synovial fluid are test results which are highly indicative of PJI. However, in patients with THA, the values of the same diagnostic test were different[13]. In research conducted by Schinsky et al. it has been proved that leukocyte values above 4200/μL and neutrophil values over 80% obtained from synovial fluid after THA are values which go in favor of confirming the presence of PJI[14].

Sonicate-fluid culture is a method which is increasingly being used in PJI diagnostics because it has proved to be a very useful means for determining a correct diagnosis. This is easy to use technique and it does not require highly sophisticated facilities to be conducted. A study has shown that higher sensitivity in PJI diagnosing using sonication-fluid culture technique (78.5%) was achieved as opposed to tissue culture (60.8%) and synovial fluid culture (56.3%) in patients with THA and TKA. We have also seen that a preoperative use of antibiotics can lower sensitivity of sonication-fluid and tissue culture[15].

In order to provide the best possible treatment, PJI have been divided into *early*, *delayed* and *late* based on the onset of symptoms after TJA (Table 1.)[16].

TABLE 1
PJI CLASSIFICATION BASED ON THEIR ONSET

Classification	Characteristics
I. Positive intraoperative cultures	At least 2 positive intraoperative cultures
II. Early postoperative infections A. Superficial; B. Deep	Less than 1 month after implantation
III. Acute hematogenous infections	Any time after implantation
IV. Late chronic infections	Any time after 1 month of implantation

Tsukayama et al.[17] also suggested the classification of PJI based on the duration of clinical symptoms of infection into: positive intraoperative cultures, early postoperative infections, acute hematogenous infections and late chronic infections (Table 2).

Because of different definitions and rules for diagnosing PJI, in 2011. a working group was formed with the aim to establish a new definition for PJI which everyone would use for PJI diagnosing. It was concluded that a PJI diagnosis can be confirmed if we have the following:

1. A fistula which connects the prosthesis with the skin surface or,
2. A confirmed pathogen in 2 or more separate tissue or fluid samples from periprosthetic area or,
3. If 4 out of 6 following conditions have been met:
   1. Elevated values of serum ESR and serum CRP,
   2. Elevated values of synovial white blood cell count,
   3. Elevated values of polymorphonuclear percentage synovial fluid,
   4. Purulence in the prosthetic joint,
   5. A confirmed pathogen in one culture of periprosthetic tissue or fluid,
   6. > 5 neutrophils per field in 5 high-power fields in a sample from histologic analysis of periprosthetic tissue at ×400 magnification.

If less than 4 conditions are met, it does not exclude the existence of PJI[18].

Imaging Studies

The first imaging diagnostic test that we perform when there is suspicion of PJI is plain radiographic imaging (two projections) of the operated joint. In a large number of cases, X-ray images show no irregularities i.e. we do not see any changes in bones. Only in a small number of those images bone resorption and bone destruction can be seen and they are shown as periprosthetic lucency. Periprosthetic lucency is characteristic for X-ray images in case of chronic infection, and very rare in case of acute infections[5]. We have to be aware that radiographic assessment is useful for showing endoprosthesis but it is not sensitive or specific for PJI[19]. If a PJI is suspected, but X-ray images are normal, a bone scan using technetium Tc99m diphosphonate is done. After injecting, scanning is performed which shows an accumulation of isotopes around the prosthesis in case of PJI. This diagnostic technique is sensitive, but not specific, so it has to be combined with some other diagnostic technique in order to make a diagnosis. We can also use leukocyte-labeled bone scan method which is more precise, but also more expensive and it

TABLE 2
PJI CLASSIFICATION BASED ON THE DURATION OF SYMPTOMS

Classification	Time of onset	Pathogen
Early infections	Less than 3 months	Most frequently caused by more virulent microorganisms (S. aureus or gram-negative bacilli)
Delayed infections	From 3 to 24 months	They are low grade infections. Caused by less virulent microorganisms (coagulase-negative staphylococci or P. acnes)
Late infections	After 24 months	They are caused by hematogenous spreading

requires much more time to perform it. Leukocytes need to be isolated from the patient's blood and labeled with radioisotopes. After labeled leukocytes are re-injected into patient's body, scanning is done immediately and 24 hours after[20].

^{18}F-fluoro-2-deoxyglucose (FDG)-PET can be used for detecting PJI because it shows glycolytic cells which form part of infection processes. Increased FDG uptake between prosthesis and bone indicates that there is an infection. The advantages of this method are its simplicity and getting results very quickly which is important for early initiation of therapy. In the research carried out by Zhuang et al. it has been proved that the sensitivity of this imaging method is 90.5% and specificity 81.1% for PJI in case of THA and TKA. Finally, the FDG PET method showed better results in detecting PJI in case of THA than in case of TKA[21].

Computed tomography (CT) enables better bone and tissue imaging compared to a plain X-ray. A disadvantage of this imaging method is bad image quality because of the presence of metal, the material which prostheses are made of. Thus, it is rarely used[22].

Magnetic resonance imaging (MRI) is an imaging test which can provide a lot of data. An advantage is that it does not use X-rays for images so exposure is reduced. The problem is that metal implants cause disturbances in images and patients who have metal implants cannot undergo this diagnostic method. Titanium and tantalum are exceptions[22].

Treatment

Antibiotic

Antibiotic therapy is an integral part of PJI treatment. It would be impossible to fight infections without it. Although antibiotics are an irreplaceable weapon in PJI treatment, one or a combination of antibiotics should be smartly chosen. If a wrong choice is made, consequences could be significant. Before any use of antibiotics, the sensitivity of the pathogen to the chosen antibiotic should be checked. Because of the possibility of resistance of bacteria to antibiotics, a combination of two antibiotics should always be kept in mind as backup in case of resistance[4]. Rifampicin is very successful in treating PJI caused by S. aureus. Studies have shown that if it is used in combination with another antibiotic (levofloxacin, linezolid), it has better results than antibiotic monotherapy. This therapy is applied only after infectious agents have been detected in the taken samples and have been tested for sensitivity to antibiotics[23]. Rifampicin is avoided as monotherapy in PJI treatment caused by S. aureus because of described possibility of developing resistance[23,24].

Chronic antibiotic suppression is a treatment method used in patients who refuse surgical treatment, who are in the terminal phase of disease or there is great danger of jeopardizing patient's life with surgical treatment. A patient with diagnosed PJI, but without a possibility to undergo surgery, needs to use oral antibiotics for life. Goal is that the patient tolerates well the chosen oral antibiotic and the pathogen is sensible to it. This treatment method will not cure infection but only alleviate pain and other clinical symptoms. This type of therapy can lead to the development of resistance[4].

Orthopedic Surgery

Irrigation and debridement include the debridement of the affected tissue, replacement of modular components, joint irrigation with physiologic fluid containing antibiotic, followed by intravenous antibiotic therapy directed towards the pathogen.

In general, acute postoperative and acute hematogenous infections are treated with irrigation and debridement while chronic infections are treated with two-stage replacement. One-stage cementless exchange is a possible alternative in case of acute postoperative infection after THA since it enables better debridement and extraction of compromised implants. The period of patient follow-up ranged from 27–89 months and the outcome was successful in 70% (19 of 27) of patients since there was no need for removing their implant[25].

After irrigation and debridement procedures the use of outpatient and home parenteral antibiotic therapy (OHPAT) for an average of 58 days has been increasing in the last few years and now it provides an efficient method for dealing with PJI. Retaining prosthesis thanks to thorough debridement and OHPAT during a longer period of time is a good option to avoid revision. A retrospective study on 14 patients has demonstrated that this combined approach has successful outcomes (70% TKA and 100% THA) in patients who were examined up to 6 month after treatment. This method has proved to be as effective as inpatient treatment; however it has significant advantages such as cost-effectiveness and patients' content with the procedures[26].

One stage procedure means that surgery is performed in one act, i.e. it includes thorough debridement, irrigation and replacement of all components of endoprosthesis. If PJI pathogen is known, antibiotic treatment is administered according to the antibiogram two to three weeks before surgery[4].

Two stage procedure includes the removal of endoprosthesis, thorough irrigation, debridement of the infected tissue and installing methyl methacrylate spacer mixed with antibiotic in the first stage [20]. The endoprosthesis is removed and we try to keep as much bone as possible for the next stage. We remove the whole cement and take samples for microbial analysis. We need to take 6 samples. Finally, in TKA we place methyl methacrylate spacer mixed with antibiotic, while in THA we do not use the spacer. Patient receives intravenous antibiotic therapy for 6 weeks followed by 6 weeks of break with regular checkups for clinical signs of infection and inflammation markers. If there are no signs of infection we can proceed with the second stage and perform re-implantation. Mahmud

et al. research reported on 253 knees with PJI treated with two-stage procedures where there was 85% success rate in 5 year life span and 78% success rate in 10 year life span[27]. If infection signs are persistent, antibiotic treatment should be continued according to the antibiogram during 12 weeks for TKA and 24 weeks for THA[4].

Girdlestone arthroplasty is an option for treating patients with THA for whom revision surgery is not an adequate solution for PJI. These are senior patients who have lesser functional demands and who would have difficulties handling more complex surgeries because of their weaker general physical condition. The advantage of this method is that it alleviates pain and helps cure PJI. Satisfaction rate in patients after this surgical treatment is 71%. A disadvantage of Girdlestone arthroplasty treatment is the subsequent shortening of extremity and obligatory use of an orthopaedic aid for walking[28].

Arthrodesis used to be performed very often in the past; however, with the development of surgical techniques and technological progress, it is less and less used in orthopaedic surgery for treating PJI. Today, it is used in patients with advanced immunodeficiency and in patients who have small functional demands[4]. It has proved to be successful in treating infection and alleviating pain but its disadvantage is that it restricts patients in their everyday activities. It should be kept in mind that it cannot be used reciprocally on all joints so the solution needs to be planned in advance. Arthrodesis can be performed with external and internal fixation. Internal fixation is most commonly done with intramedullary nail which gives very good results[20].

Amputation is left as the last resort when all other options have been exhausted. We decide to use this kind of surgical treatment when patient's life is in danger because of possible development of sepsis or impossibility of eradicating the source of infections[20].

Conclusion

To conclude, a lot remains to be clarified both in PJI diagnostics and treatment. Many conclusions and assumptions are based on small scale studies and insufficiently investigative protocols. There are too many opposing studies where physicians have to decide based on their knowledge, experience and judgment on which protocol seems most adequate. A lot of effort is being invested in researching and clarifying the unknowns surrounding PJI. If we look into our recent past, it will be clear how much progress has been made in fighting PJI. Day after day we have better conditions to fight against PJI.

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INFEKCIJE OKO PROTEZE NAKON TOTALNE ARTROPLASTIKE KUKA I KOLJENA

S A Ž E T A K

Infekcije zgloba oko proteze (PJI) u ortopedskoj kirurgiji se smatraju vrlo ozbiljnim i opasnim komplikacijama totalne artroplastike. PJI postaje dugotrajan medicinski problem i težak teret za pacijenta i njegovu obitelj. Pacijenti s takvom komplikacijom su značajan teret i za zdravstveni sustav. Prepoznajući ovaj problem, investiranje u znanstvena istraživanja i istovremeni razvoj tehnologija u medicini predstavljaju napore za povećanjem uspješnosti prevencije i liječenja PJI. Svake godine se broj totalnih artroplastika povećava, što utječe i na porast broja komplikacija, među kojima su vodeće infekcije. Ponekad, u najgorem slučaju, infekcije mogu ugroziti život pacijenta. Novi proceduralni algoritmi i nove dijagnostičke mogućnosti nam pomažu u postavljanju precizne i rane dijagnoze postoperativne PJI s velikim stupnjem sigurnosti. Te dijagnostičke metode uključuju laboratorijske testove, slikovnu dijagnostiku, histopatologiju i mikrobiološke analize. Mogućnosti liječenja ovise o brojnim čimbenicima, koji uključuju pojavu simptoma, opće fizičko stanje pacijenta i tip patogena. Pristup liječenju PJI je kompleksan i zahtijeva multidisciplinarni pristup, kako bi se osiguralo najuspješnije moguće liječenje. Za prikladno i uspješno liječenje moramo uzeti u obzir antibiotsku terapiju, jednostupanjsku ili dvostupanjsku reviziju, operaciju po Girdlestone-u, artrodezu i amputaciju. U ovom pregledu pokušat ćemo prikazati sva relevantna postignuća i predložiti daljnje korake u zbrinjavanju PJI.