Hong Kong Journal of Orthopaedic Research
(An Open Access Journal for Orthopedics and Trauma Research)

Research Article

Hong Kong J Orthop Res
2021; 4(3): 69-73
ISSN (e): 2663-8231
ISSN (p): 2663-8223
Received: 27-07-2021
Accepted: 29-10-2021

www.hkorthopaedicjournal.com
DOI: 10.37515/ortho.8231.4303

Periprosthetic joint infections: A 20 years retrospective epidemiological study in a single european accademic hospital

Alfonso Manzotti[1], Miriam Grassi[1], Marco Mattia Larghi[2], Francesca Moioli[1], Davide Brioschi[1]

1 *Orthopaedic and Trauma Department, ASST Fatebenefratelli Sacco, University Hospital "Luigi Sacco", Via GB Grassi, 74; Milan, 20157, Italy*

2 *School of Medicine and Residency Program in Orthopaedics, Università degli Studi di Milano, Italy*

Abstract

Introduction: Periprosthetic Joint infections (PJIs) still represent one of the most challenging complications in orthopaedic reconstructive surgery. The aim of our work is to present a retrospective observational analysis with 20 years of follow up of PJIs referred to a single center equipped with a regional referral infectious diseases department. **Materials and methods:** 368 case of deep PJIs following a primary or revision hip and knee arthroplasty procedure referred to our center between January 1996 and December 2016 were included in the study. Criteria of inclusion in the study was a primary PJI entirely managed in our hospital. We collected demographic data, risk factors, microbiology (identification pathogenic agent), previous surgical treatments, type of implant, diagnostic criteria of infection, type of infection and medical or surgical treatments performed in our institution **Results:** A total of 200 (54,3%) infection occurs in hip arthroplasty and 168 (45,7%) in knee arthroplasty. Mean age was 64,7 years. The majority were late infections (58,8%). Respectively polymicrobial infections was identified in 83 (22,6%) cases and in 54 (14,7%) patients no isolation was possible. S. Aureus was the most frequently identified pathogen. The major risk factors were hypertension in 254 (69,1%), cardiovascular diseases in 167 (45,7%), obesity in 97 (26,5%) and diabetes mellitus in 92 (25%). **Discussion:** Epidemiological analysis of PJI in our hospital which collects data relating to the last 20 years, has permitted to obtain a summary of our scenario. Ideal PJI management should include an accurate patient history considering carefully risk factors, patients conditions, and previous surgical procedures ideally in a multispecialist enviroment.

Keywords: Epidemiology, Hip arthroplasty, Knee arthroplasty, Periprosthetic joint infection.

INTRODUCTION

Periprosthetic joint infection (PJIs) incidence following hip and knee arthroplasty have been reported in literature to be around 1-2,5% [1, 2, 3, 4]. Bacteria and less frequently fungi and mycobacteria can colonized and adhere to the implant via hematogenous dissemination or directly during surgery creating a polysaccharidic biofilm not permeable to both immunological response and antibiotic activity [1, 3]. Micro-organisms more frequently causing PJI in the United States are Staphylococcus aureus and Staphylococcus epidermidis, in Europe coagulase negative Staphylococcus, Enterococcus, Streptococcus and Gram negatives with the Propionibacterium acnes as the most frequent isolated anaerobic bacteria in PJI [5, 6]. Several definitions of PJIs have been suggested in literature until 2018 when an International Consensus Meeting (ICM) published well restricted definitions, based on major and minor criteria (Table 1) [7-13].

Likewise in literature patient-related and procedure-related factors have been reported as increasing risk to develop PJIs such as tobacco use, diabetes mellitus, obesity, corticosteroid use, psoriasis, rheumatoid arthritis, a history of bone cancer, immune system deficiencies, revision surgery and operating time [14-15].

By 2020 the cost of treating PJIs in the United States is estimated to be around $ 1,62 billion with 60,000-70,00 knee and hip arthroplasties will require treatment for PJI and similarly even in some European country it has been estimated an annual increase of 5% of costs related to PJI [1, 2, 16, 17].

In the majority of western country a national arthroplasty registry is available collecting data on surgical procedures and explaining reason of implant failures including PJI. However just reporting PJI incidence is not sufficient to well define clear PJI epidemiological guidelines including correct prophylaxis especially in countries with different microbiological epidemiology and with a high rate of multidrug resistant pathogen.

***Corresponding author:**
Dr. Miriam Grassi
Orthopaedic and Trauma Department, ASST Fatebenefratelli Sacco, University Hospital "Luigi Sacco", Via GB Grassi, 74; Milan, 20157, Italy.
Email: grassi.miriam@asst-fbf-sacco.it

Aim of this retrospective epidemiologic study was to describe a 20 years complete scenario of knee and hip PJIs primarily managed in a single academic hospital equipped with a regional referral infectious disease department in a metropolitan European area to suggest proper multispecialist guidelines in managing these complex cases.

MATERIALS AND METHODS

Assessing retrospectively the Hospital Discharge Forms between January 1996 and December 2016 and using ICDM-9-CM classification (code 996.66) corresponding to infection and inflammatory reaction from hip and knee prosthesis, we selected all the deep PJIs managed in a single academic hospital equipped with a regional referral infectious disease department in a metropolitan European area, in Northern Italy.

As a reference center for infection diseases our hospital receives multiple patients, often following multiple failures, with a treatment for PJI already started in other hospitals making the epidemiological scenario not objective. On this purpose, to avoid any bias influencing the epidemiological sample, we included in the study only patients affected by a PJI following a primary or revision arthroplasty procedure entirely identified and treated in our hospital. Patients referred to our hospital for any treatment with already a confirmed diagnosis of PJI and patients with a diagnosis of PJI ruled out in our institution but having a treatment in another center or with incomplete data were excluded. According to these strict criterias 368 patients were eligible in our study from a population of 407 patient with diagnosis of infection and inflammatory reaction from hip and knee prosthesis.

We collected demographic data, clinical data, surgical data and microbiological data creating an 4 sections database including:

- section 1: age, sex, original diagnosis requiring replacement and commorbities affecting the patients;

- section 2: previous surgical treatments, site and type of implant;

- section 3: presence of infection criteria according to 2013 Philadelphia International Consensus Meeting (ICM), infection occurance, pathogenic agent;

- section 4: medical or surgical treatments.

Primary surgical procedure were registered implant features according if partial (hemiarthroplasty and unicompartimental) or total arthroplasty and type of fixation (cemented or uncemented). According to Philadelphia International Consensus Meeting PJI infection criteria were registered as either major or minor (Table 1) and assuming a diagnosis of PJI when either one of the major criteria or simutaneosuly 5 minor criteria were present despite a missing pathogen identification [7-13]. PJI were furtherly classified according to the occurrence criteria according to Zimmerli *et al.* and divided in early (occurred during the first 3 months post-surgery), delayed (occurred between 3 to 24 months after surgery) and late infections (occurred more than 24 month after surgery) [10]. All patients include in the study had at least a blood and/or a synovial fluid cultures obtained before and during surgery if surgically managed. Routinely during the surgical procedure a minimum of 5 specimens were taken from each joint and sent for anaerobic/aerobic, fungal and acid-fast bacteria culture growth. Cultures were all incubated in appropriate conditions till possible germ identification for a maximum of 14 days and all the identified pathogen were collected. Finally antibiotic therapies, considering both the pharmacological class and the mean of pharmacological cycles as well as surgical procedures types and numbers, were all collected.

Table 1: Definition criteria of periprosthetic joint infection according to the International Consensus Group on Periprosthetic Joint Infection

Major criteria	Two positive periprosthetic cultures with phenotypically identical organisms OR a sinus tract communicating with the joint.
Minor criteria	Elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip OR Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%), Positive histological analysis of periprosthetic tissue, a single positive culture.

Statistical Analysis

Statistical processing was carried out with SPSS (Statistical Package for Social Science) (IBM SPSS, Chicago, IL, USA), version 11.0, with a level of nominal significance of $p \leq 0,05$. All analyses were performed by SPSS 17.0 (IBM SPSS, Chicago, IL, USA).

RESULTS

The demographic data are collected in table 1 with a mean of 136 (37,1%) males patients and 232 (62,9%) females and the mean age was 74.7 years (range 63-81) (Figure 1). There were 312 primary arthroplasties and 56 revision procedures with respectively the following diagnosis leading to the original reconstructive procedure: primary osteoarthritis in 223 (60.1%), post-traumatic arthritis in 68 (18,4%) patients, aseptic mobilization with device failure in 54 (14,7%), congenital hip dysplasia in 7 (2%), femoral avascular necrosis in 11 (4.4%), previous septic arthritis in 5 (1,4%). Likewise there were 238 (64.7%) cemented implants were cemented and 130 (35.3%) not cemented.

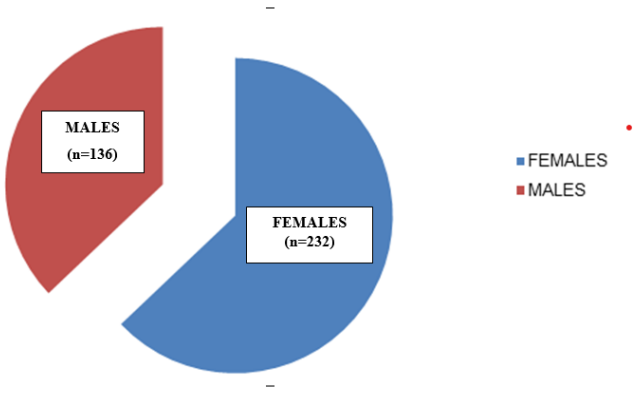

Figure 1: Sex distribution in our cohort

The patients reported respectively hypertension in 254 (69,1%) patients, cardiovascular diseases in 167 (45,6%), obesity (body mass index>35) in 88 (26,5%), type 2 diabetes in 82 (25%), any neoplastic disease in 59 (16,2%), long-term corticosteroid use in 37 (10,3%), any other immunosuppression in 22 (8,8%), alcohol abuse in 7 (3%) and rheumatoid arthritis in 5 patients (1,5%) with 257 (70%) of the all the patients referring simultaneously at least 2 comorbities (Table 2) and 102 (40%) of the all the patients referring previous replacement. The median BMI value of our sample was 26,75 Kg/m2.

Table 2: Prevalence of risk factors for PJIs in our sample

Risk factors	%	n
Hypertension	69	254
Cardiovascular disease	45,6	167
Diabetes	25	82
Chronic steroid use	10,3	37
Cancer	16,2	59
Immunosoppression	8,8	22
Alcohol abuse	3	7
Rheumatoid arthritis	1,5	5
Previous replacement	40	102
Obesity	26,5	88

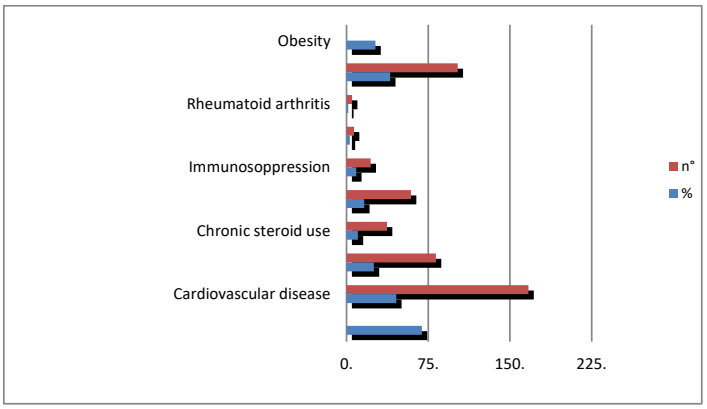

Figure 2: Risk factors distribution in our cohort

PJI was identified were respectively in 200 (54,3%) hip arthroplasty and in 168 (45,7%) in knee arthroplasty, with 35 (17,7%) partial hip replacement and 16 (9,5%) partial knee replacement. According ICM criteria in 169 (46%) cases, PJI diagnosis was based on identification of one major criteria and in 199 (54%) because the concomitant presence of 3 minor criteria. According to Zimmerli classification, we divided PJI respectively in late infections in 216 patients (58,8%), early infections in 121 patients (33%) and delayed infections in 30 patients (7,9%) [11].

We could not identified any pathogens in 54 patients (14.7%), a single pathogen in 231 patients (62,7%) and a polymicrobial flora in 83 patients (22,6%) (Table 3). Staphylococcus aureus (MSSA) was identified in 107 (28%) patients, a coagulase negative Staphylococcus in 66 (18%) patients, Gram negative microorganisms in 59 (16%) patients, Staphylococcus aureus (MRSA) in 33 (9%) patients, Gram positive microorganisms in 33 (9%) patients and Staphylococcus aureus Vancomycin resistant in 14 (3,5%) patients.

Table 3: Prevalence of microbiological agent in our cohort

Isolate	%	N
Polymicrobial flora	22,6	83
Staphylococcus aureus (MSSA)	28,6	107
Staphylococcus coagulase negative	18,7	66
Gram negative microorganism	15,8	59
Staphylococcus aureus (MRSA)	9	33
Gram positive microorganism	9,7	33
Staphylococcus aureus Vancomycin resistant	3,5	14
No isolation	14,71	54

In our institution all surgeries were performed by 4 experienced, specialty-trained hip and knee surgeons, with greater than 10 years experience.

In our group 332 (90%) of the patient s underwent to a surgical procedure always in association with antibiotic therapy, while in the remaining 36 (10%) of cases received only a soppressive antibiotic therapy because either medical contraindication to any further surgical procedure or a patient refusal to any surgical procedure. The median of antibiotic therapy was approximately 4.3 weeks for patients undergoing one-stage revision, approximately 3.7 weeks pre-operative and then approximately 8.5 weeks between first surgery and second surgery in patients undergoing two-stage revision and approximately 1.2 weeks for patients undergoing DAIR. We performed respectively joint debridement in association with antibiotics and implant retaining (DAIR) in 173 (47%) of cases, a 2-stages revision in 147 (40%) and a 1 stages arthrodesis in 11 (3%). DAIR was adopted in all the 3 infection categories: 115 (66% of all all DAIRS) in early infection (within 3 months from occurrence) and 3(1%) and 55 (31%) respectively in late and delayed infection. Two stage revision was performed equally in both late delayed infection. Surprisingly one of the cases of arthrodesis was adopted in an early infections case because multiple progressive failures.

Table 4: Prevalence of surgical and therapeutic approach

Treatment	Percentage of cases	N
Soppressive antibiotic therapy	10%	36
Debridement and wash-out	47%	173
Prosthetic revision in 2 steps	40%	147
Prosthetic revision in 2 steps with arthrodesis	3%	12

The most common prescribed antibiotic classes were glycopeptides in 30% of the overall antibiotic treatments cases, beta-lactams in 21%, quinolone antibiotics in 17%, rifampicin in 11%, carbapenems in 8%, aminoglycosides in 5%, co-trimoxazole in 5%, lipopeptides in 3%, oxazolidinones in 1.5% and lincosamides in 1.5% of the overall antibiotic treatments.

According to univariate and multivariate logistic regression analysis our data showed that the risk of an early infection onset is equal to 1,05 (95% CI: 1.015-1.110; P-Value = 0.057) times higher for each year of patient's age, the risk of infection by Gram negative microorganisms is 6,33 (95% CI: 2.006-18.627; P-Value < 0.05) times higher for each year of patient's age

DISCUSSION

PJI represents one of the most fearful complications of prosthetic surgery, being responsible for high morbidity because of complex surgical and medical treatments with enormous healthcare costs [1-6]. Dedicated risk assessment scales for PJI development have been recently proposed by several authors, in order to identify pre-operatively the patients with a higher risk of post-operative PJI with no general agreement on which of this scores could be considered the most reliable ones [18, 19]. Likewise in literature several authors identified significant PJI risk factors, differentiating them between strong and moderate risk as well as defining patient related factors without any significance [12-21]. Between non-significant patient related factors have been suggested age, elevate alcohol intake, osteonecrosis, primary and post-traumatic osteoarthritis, cardiovascular disease and arterial hypertension.

Commonly an increased BMI, previous corticosteroid therapy, previous joint surgery (primary or revision) have been definited as major factors

predisposing to PJIs while diabetes mellitus, rheumatoid arthritis, malignancy history, immunosuppression, smoke as common moderate factors [12-21].

In literature several previous studies reported epidemiological analysis of PJI mainly involving several different centers [20, 21]. In 2020 Mussa *et al*. published an epidemiological study performed in a single center in a period of 7 years enrolling all the patients referred to an academic hospital [22]. Despite the strict protocol they did not clearly mention if both the responsible pathogen was already identified somewhere else and if all the treatments were completed in their own center. Furthermore in their study there is no mention about both surgical patients history, and clinical PJI identification criteria adopted.

Our study was performed in a single hospital equipped by a referral infectious disease department including only selected hip and knee PJI identified and treated by a single team over a period of 20 years. We conducted a detailed analysis gathering surgical, microbiological and epidemiological data with the aim of establishing a PJI scenario in our institution to improve strategies designed to reduce the risk of PJI.

All the patients in our study were older than 63 years and the great majority (79%) received arthroplasty in a NHS hospital. Our univariate and multivariate analyses showed a correlation between increasing age and early onset PJI with Gram-negative isolation. This observation can correspond to similar findings in studies describing the epidemiology of isolated pathogens from PJI and osteoarticular infections in older aged patients [23]. The prevalence of female gender in our sample highlights that, in our scenario, arthroplasty surgery is more performed in women, who undergo hip and knee prosthetic surgery 1.5 times more than men. Basing on current literature this cannot be considered a risk factor [24, 25]. We would like to underline that at the time of diagnosis, 48 (70%) of our patients referred at least 2 or more comorbidities arising clearly some obvious correspondences between patient health status and PJI risk.

Both arterial hypertension and cardiovascular disease are well represented in our cohort of patients, even if they are not universally considered risk factors of PJI in literature. They could be considered risk factors only when associated with diabetes which is quite common in elderly population [26]. Actually, a meta-analysis has indicated coronary artery disease as risk factor [27]. One explanation suggested was related to anticoagulation and/or antiplatelet therapy and its relationship with an increased risk for infections.

The 13% of our patients were smokers and Møller *et al*. already suggested that a smoking cessation programs starting 6 to 8 weeks before surgery could reduce postoperative several complications in patients undergoing THA or TKA [28].

In our sample we assessed hip PJI in 54,4% cases and knee PJI in 45,6%. These results show an almost equal distribution between infection sites coherent with current our country epidemiology [22, 29]. Likewise in our study in hip PJIs occurred more frequently in total arthroplasty (59,5%) than in hemiarthroplasty (40,2%). This aspect was even more evident in knee with 83,7% of the case involving total knee replacements and only 16,1% involving unicompartimental replacements showing a direct e impact with surgical procedure invasivity.

In our study we registered a greater percentage of late PJIs 58,8% in discordance with literature, where it has been reported that the most frequent PJIs are those with early and delayed onset [29, 30]. A possible explanation could be related to both a poorer diagnostic protocols in the first cases and to our patients surgical history of with a mean of 2 previous surgical procedures.

In 14,71% of our case we could not identified a pathogen despite diagnosis was performed according to strict ICM clinical criteria and this data is in accordance with other similar reports in literature obtained even with sonification support [22]. More commonly in our patients we registered PJI caused by polymicrobial floras with a Methicillin-Sensitive Staphylococcus Aureus (MSSA) as the most common germ in discordance with other reports suggesting coagulase-negative staphylococci as the pathogens more frequently responsible for PJI in Europe [31-33]. A possible explanation could be the higher number of early and late, more frequently caused by MSSA, in our group. Furthermore Drago *et al*. already reported a higher polymicrobial infections with multidrug-resistant pathogens just in late infections [32].

Regarding the therapeutic management, a combined antibiotic and surgery treatment was adopted in 89.71% of the patients, while, in the remaining 10.29% received only a chronic suppressive antibiotic therapy because poor health status in accordance both with the Italian Infection Study Group Gruppo (GISIG) and the Infection Diseases Society of America (IDSA) [6, 11, 12, 31, 33]. In our series DAIR was the most represented surgical procedure for the early PJI showing a success rate ranging between 50% and 91.7% within 4-8 weeks from infection onset [34-36]. In delayed and late onset infections the most frequently surgical approach adopted by our unit was the two-stage surgery, considered a gold standard procedure by several authors and the best option for difficult-to-threat pathogens [32]. Literature data regarding 2 stages revision showed a successful outcome in over 90% of cases and a reinfection rate about 7.9% in patients with more than three comorbidities [31-33].

Two stages arthrodesis was adopted only in a few of cases following multiple failure as a definitive treatment in patients with already compromised joint functionality.

We adopted antibiotic suppressive treatment only for patients either not suitable for surgery because a high life risk or for patients who refused surgery.

Our study is evidently limited by its retrospective design and small number of cases analysed.

CONCLUSION

In the next future PJI incidence will increase because of growing numbers of implant procedures in aging people with remarkable economic consequences on the health care systems. Epidemiological analysis of PJI in our hospital which collects data relating to the last 20 years, has permitted to obtain a summary of our scenario, allowing us to draw organism profile responsible for PJI and the to identify the most suitable strategies for the prevention and treatment of these infections. Health care systems needs to invest in obtaining a more accurate, earlier, diagnosis and history. This aspect can lead to a more effective treatment, reducing the numbers of complex and more risky procedure, decreasing long periods of hospitalization and immobilization and sparing energies and resources. Our study confirms the high prevalence of staphylococci in PJIs as already highlighted in Literature by Aggarwal *et al*. and Mussa *et al*. [23, 29]. New prospective studies would be needed for the future to clarify the microbiological features of PJIs in Italy, with a view to the creation of a national register.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

There is no funding source.

REFERENCES

1. Pulido L, Ghanem E, Joshi A, Purtill JJ, Parvizi J. Periprosthetic joint infection: the incidence, timing, and predisposing factors. *Clin Orthop Relat Res*. 2008; 466(7):1710-1715. doi:10.1007/s11999-008-0209-4.

2. Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. *J Arthroplasty*. 2012; 27(8 Suppl):61-5.e1. doi:10.1016/j.arth.2012.02.022.
3. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. *Lancet*. 2016; 387(10016):386-394. doi:10.1016/S0140-6736(14)61798-0.
4. Poultsides LA, Liaropoulos LL, Malizos KN. The socioeconomic impact of musculoskeletal infections. *J Bone Joint Surg Am*. 2010; 92(11):e13. doi:10.2106/JBJS.I.01131.
5. Shah NB, Tande AJ, Patel R, Berbari EF. Anaerobic prosthetic joint infection. *Anaerobe*. 2015; 36:1-8. doi:10.1016/j.anaerobe.2015.08.003.
6. Chen AF, Heller S, Parvizi J. Prosthetic joint infections. *Surg Clin North Am*. 2014; 94(6):1265-1281. doi:10.1016/j.suc.2014.08.009.
7. Workgroup Convened by the Musculoskeletal Infection Society. New definition for periprosthetic joint infection. J Arthroplasty. 2011 Dec; 26(8):1136-8. doi: 10.1016/j.arth.2011.09.026. PMID: 22075161.
8. Parvizi J, Gehrke T, Chen AF. Proceedings of the International Consensus on Periprosthetic Joint Infection. *Bone Joint J*. 2013; 95-B(11):1450-1452. doi:10.1302/0301-620X.95B11.33135.
9. Parvizi J, Shohat N, Gehrke T. Prevention of periprosthetic joint infection: new guidelines. *Bone Joint J*. 2017; 99-B(4 Supple B):3-10. doi:10.1302/0301-620X.99B4.BJJ-2016-1212.R1.
10. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med*. 2004; 351(16):1645-1654. doi:10.1056/NEJMra040181.
11. Parvizi J, Tan TL, Goswami K, *et al*. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. *J Arthroplasty*. 2018; 33(5):1309-1314.e2. doi:10.1016/j.arth.2018.02.078.
12. Abdelaziz H, Rademacher K, Suero EM, *et al*. The 2018 International Consensus Meeting Minor Criteria for Chronic Hip and Knee Periprosthetic Joint Infection: Validation From a Single Center. *J Arthroplasty*. 2020; 35(8):2200-2203. doi:10.1016/j.arth.2020.03.014.
13. Zhu Y, Zhang F, Chen W, Liu S, Zhang Q, Zhang Y. Risk factors for periprosthetic joint infection after total joint arthroplasty: a systematic review and meta-analysis. *J Hosp Infect*. 2015; 89(2):82-89. doi:10.1016/j.jhin.2014.10.008.
14. 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):529-536. doi:10.1111/iwj.12640.
15. Maoz G, Phillips M, Bosco J, *et al*. The Otto Aufranc Award: Modifiable versus nonmodifiable risk factors for infection after hip arthroplasty. *Clin Orthop Relat Res*. 2015; 473(2):453-459. doi:10.1007/s11999-014-3780-x.
16. Torre M, Luzi I, Masciocchi M, Zanoli G, Tranquilli Leali P, Leone L Il registro Italiano Artroprotesi (RIAP): Stato dell'Arte. GIOT 2013; 39:90-95.
17. Iorio R, Williams KM, Marcantonio AJ, Specht LM, Tilzey JF, Healy WL. Diabetes mellitus, hemoglobin A1C, and the incidence of total joint arthroplasty infection. *J Arthroplasty*. 2012; 27(5):726-9.e1. doi:10.1016/j.arth.2011.09.013.
18. Signore A, Sconfienza LM, Borens O, *et al*. Consensus document for the diagnosis of prosthetic joint infections: a joint paper by the EANM, EBJIS, and ESR (with ESCMID endorsement) [published correction appears in Eur J Nucl Med Mol Imaging. 2019 Feb 9;:]. *Eur J Nucl Med Mol Imaging*. 2019; 46(4):971-988. doi:10.1007/s00259-019-4263-9.
19. Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD. Systematic review of risk prediction scores for surgical site infection or periprosthetic joint infection following joint arthroplasty. *Epidemiol Infect*. 2017; 145(9):1738-1749. doi:10.1017/S0950268817000486.
20. Stryker LS, Abdel MP, Morrey ME, Morrow MM, Kor DJ, Morrey BF. Elevated postoperative blood glucose and preoperative hemoglobin A1C are associated with increased wound complications following total joint arthroplasty. *J Bone Joint Surg Am*. 2013; 95(9):808-S2.
1. 21.Kunutsor SK, Whitehouse MR, Blom AW, Beswick AD; INFORM Team. Patient-Related Risk Factors for Periprosthetic Joint Infection after Total Joint Arthroplasty: A Systematic Review and Meta-Analysis. *PLoS One*. 2016; 11(3):e0150866. Published 2016 Mar 3. doi:10.1371/journal.pone.0150866.
21. Drago L, De Vecchi E, Bortolin M, Zagra L, Romanò CL, Cappelletti L. Epidemiology and Antibiotic Resistance of Late Prosthetic Knee and Hip Infections. *J Arthroplasty*. 2017; 32(8):2496-2500. doi:10.1016/j.arth.2017.03.005
22. Mussa M, Manciulli T, Corbella M, *et al*. Epidemiology and microbiology of prosthetic joint infections: a nine-year, single-center experience in Pavia, Northern Italy [published online ahead of print, 2020 Jan 28]. *Musculoskelet Surg*. 2020; 10.1007/s12306-020-00638-y. doi:10.1007/s12306-020-00638-y.
23. Hsieh PH, Lee MS, Hsu KY, Chang YH, Shih HN, Ueng SW. Gram-negative prosthetic joint infections: risk factors and outcome of treatment. *Clin Infect Dis*. 2009; 49(7):1036-1043. doi:10.1086/605593.
24. Resende VAC, Neto AC, Nunes C, Andrade R, Espregueira-Mendes J, Lopes S. Higher age, female gender, osteoarthritis and blood transfusion protect against periprosthetic joint infection in total hip or knee arthroplasties: a systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2021 Jan; 29(1):8-43. doi: 10.1007/s00167-018-5231-9. Epub 2018 Nov 9. PMID: 30413860.
25. Inoue D, Xu C, Yazdi H, Parvizi J. Age alone is not a risk factor for periprosthetic joint infection. *J Hosp Infect*. 2019; 103(1):64-68. doi:10.1016/j.jhin.2019.04.005
26. Triantafyllopoulos GK, Soranoglou VG, Memtsoudis SG, Sculco TP, Poultsides LA. Rate and Risk Factors for Periprosthetic Joint Infection Among 36,494 Primary Total Hip Arthroplasties. *J Arthroplasty*. 2018; 33(4):1166-1170. doi:10.1016/j.arth.2017.11.040.
27. Bozic KJ, Lau E, Kurtz S, Ong K, Berry DJ. Patient-related risk factors for postoperative mortality and periprosthetic joint infection in medicare patients undergoing TKA. *Clin Orthop Relat Res*. 2012; 470(1):130-137. doi:10.1007/s11999-011-2043-3
28. Møller AM, Villebro N, Pedersen T, Tønnesen H. Effect of preoperative smoking intervention on postoperative complications: a randomised clinical trial. *Lancet*. 2002; 359(9301):114-117. doi:10.1016/S0140-6736(02)07369-5.
29. Aggarwal VK, Bakhshi H, Ecker NU, Parvizi J, Gehrke T, Kendoff D. Organism profile in periprosthetic joint infection: pathogens differ at two arthroplasty infection referral centers in Europe and in the United States. *J Knee Surg*. 2014; 27(5):399-406. doi:10.1055/s-0033-1364102.
30. Corvec S, Loiez C *et al*: Bone and Joint infections. In European manual of Clinical microbiology, 1st Ed.Editors: Cornaglia G. Courcol R, Herrmann JL, Kahlmeter G, Peigue-Lafeuille H, Vila J, 2012b, pp227-34.
31. Leone S, Borrè S, Monforte Ad, *et al*. Consensus document on controversial issues in the diagnosis and treatment of prosthetic joint infections. *Int J Infect Dis*. 2010; 14 Suppl 4:S67-S77. doi:10.1016/j.ijid.2010.05.005.
32. Drago L, Signori V, De Vecchi E, Vassena C, Palazzi E, Cappelletti L, Romanò D, Romanò CL. Use of dithiothreitol to improve the diagnosis of prosthetic joint infections. J Orthop Res. 2013 Nov; 31(11):1694-9. doi: 10.1002/jor.22423. Epub 2013 Jul 2. PMID: 23817975.
33. Osmon DR, Berbari EF, Berendt AR, *et al*. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013; 56(1):e1-e25. doi:10.1093/cid/cis803.
34. Romanò CL, Manzi G, Logoluso N, Romanò D. Value of debridement and irrigation for the treatment of peri-prosthetic infections. A systematic review. Hip Int. 2012 Jul-Aug; 22 Suppl 8:S19-24. doi: 10.5301/HIP.2012.9566. PMID: 22956381.
35. Kuiper JW, Willink RT, Moojen DJ, van den Bekerom MP, Colen S. Treatment of acute periprosthetic infections with prosthesis retention: Review of current concepts. *World J Orthop*. 2014; 5(5):667-676. Published 2014 Nov 18. doi:10.5312/wjo.v5.i5.667.
36. Kuiper JW, Vos SJ, Saouti R, *et al*. Prosthetic joint-associated infections treated with DAIR (debridement, antibiotics, irrigation, and retention): analysis of risk factors and local antibiotic carriers in 91 patients. *Acta Orthop*. 2013; 84(4):380-386. doi:10.3109/17453674.2013.823589.