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Diagnosis and Management of orthopedic implants biofilm-related infections

summary

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Contents

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THEORETICAL PART

1. INTRODUCTION - BRIEF HISTORY OF BACTERIAL BIOFILM AND OF THE BIOFILM-ASSOCIATED INFECTIONS.

Bacterial biofilm is defined as "an aggregate of microbial cells surrounded or embedded by a polymeric matrix, that could be mono- or pluribacterial". The bacterial biofilm may or may not be adherent to surfaces, it is predominantly found in tissues or biological fluids, at the same time the presence of host components in its structure could also be possible (1).

In medicine, Niels Nøibi observes for the first time the link between the etiology of the chronic bacterial infections and the bacterial aggregates, between 1970 and 1972, through routine microscopic examinations of sputum smears harvested from patients with cystic fibrosis, smears that were Gram-stained, in patients with chronic lung infections with *Pseudomonas aeruginosa*, but also from lung specimens taken from patients who died of chronic lung infections with *Pseudomonas aeruginosa* (autopsy samples), between 1974 and 1978.

1977 is the year in which an image of a biofilm was published for the first time, an image that highlighted a bacterial aggregate surrounded by a slime, slime that would be known later as the extracellular polymeric substance (2).

J. W. Costerton, a microbiologist and professor at the University of Calgary, Alberta, Canada, has published numerous observational studies of the cell wall structure of Gram-negative bacteria. The group of researchers under the coordination of Costerton publishes in 1980 the study on tissue specimens harvested post-mortem from patients with cystic fibrosis, study that highlights the presence of microcolonies of *Pseudomonas aeruginosa* and studies the bacterial glycocalyx in natural conditions and in case of disease, a term that he replaces it in its subsequent study with the term BIOFILM (2) (4) (5) (6) (7).

2015 represents the year in which the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) published its first guideline for the diagnosis and management of biofilm-related infections.

It can be concluded that the study of bacterial aggregates surrounded by a matrix produced by them, aggregates either adherent to a surface or located into the tissues or biological fluids, is as old as microbiology, BUT the concept of infection associated with bacterial biofilm and its importance in medicine especially in chronic bacterial infections is less than 50 years. With the understanding of this concept it was also accepted both the importance and frequency of biofilm-related infections, thus appearing guidelines for diagnosis, treatment, and prevention of these types of infections (2).

2. BACTERIAL BIOFILM – AN EMERGING BACTERIAL FORM OF LIFE.

The biofilm represents a structure composed of bacterial cells (belonging to one or more species of microorganisms), an aggregate of microorganisms, in which the cells are surrounded by a self-produced matrix by bacteria, a structure in which the bacterial cells adhere to each other and/or to a surface (8).

The matrix consists of self-produced polymeric compounds, compounds that ate known as extracellular polymeric substance (EPS) or exopolysaccharides such as: polysaccharides, proteins, acids, lipids, and extracellular DNA (eDNA) (8). The term "aggregate" is used to describe that most cells are in contact with other cells forming aggregates, either attached to the surface, in which case only one layer of the structure is in direct contact with the surface, or in flakes, which are mobile biofilms, biofilms which are formed in the absence of a substrate/surface. Through social and physical cell-to-cell interaction systems together with the properties of the matrix, biofilm certainly represents a distinct form of bacterial cell life (9). Bacterial biofilm is one of the most widespread and successful life forms on Earth, being engaged in various cyclic biochemical processes in water, soil, sediments, and underground environments (9).

The biofilm is involved in various technological processes such as filtering drinking water, degradation of wastewater and solid waste, chemical production, and biofuel production. Humans can be colonized by microorganisms (bacteria or fungi) that form biofilms, cases in which they can be associated with persistent or chronic infections. Over 65% of infections are biofilm-related infections (10). Every year, in the United States, more than 12 million cases of infection are biofilm-related, the most common being associated with orthopedic implants (endoprosthesis) (11). However, biofilms are also responsible for the biofouling and contamination of treated water, and are responsible for the deterioration of drinking water and also have an influence on the corrosion process (9).

On a small scale, bacterial biofilms can be seen as biogenic habitat formers. Through the process of generating a network, bacteria in biofilms create a physically distinct habitat with different functions, such as creating a shelter, a habitat that facilitates the accumulation of nutrients and physicochemically modifies the environment in the biofilm, and also interactions between organisms in the biofilm (9).

3. CURRENT TRENDS IN THE STUDY OF BACTERIAL BIOFILM.

Surgical interventions that combine the use of implants aims to increase the patient's quality of life and health, but despite aseptic methods and antibiotic prophylaxis during the implantation of these devices, bacterial infections definitely still remain a problem. Persistent infections can lead to serious consequences even when removing the implant, consequences that involve significantly increase the healthcare assistance costs. Infections associated with implants increase the length of hospitalization and the cost of treatment of these patients. In general, the bacteria involved in this type of infection that are associated with implants have as a reservoir the skin of patients and are mobilized during implantation procedures, or through continuity solutions, or by hematogenous inoculation (40) (41) (42).

The initial bacterial adhesion is followed by a process of a gradual development of the biofilm, a process that is a primary factor of virulence of the bacteria that are involved in implants associated infections. A key feature of these bacterial communities surrounded by a matrix is their tolerance to antibiotics and to the host's mechanism of phagocytosis. Low antibiotic penetration, nutrient limitation, slow growth, adaptive response to external stress, low metabolic activity, and persistence (persistent cells) are all hypotheses that contribute to a multifaceted microbial response of the biofilm (40).

To improve the diagnosis of orthopedic implants biofilm-associated infections, it is important not only to investigate the value of the new diagnostic methods or tests but also to re-evaluate fundamental approaches, including the optimal specimen type or sample combination, appropriate culture media, and growth conditions (period, temperature, etc.). Taking into consideration that the microbiological profile of each implant-associated infection differs depending on the location of the implant, the material, and the surface characteristics, optimal specimens and diagnostic methods definitely will vary. Therefore, more than one method may be required when culture results are negative in the context of clinical suspicion of a biofilm-associated infection. The key to the optimal diagnosis of implant-associated infections is a combination of several diagnostic tools interpreted alongside the individual patient's personal history. Fluorescence in situ hybridization is the only method that - in the true sense of the word - looks at infection in situ to diagnose a biofilm infection and is often able to put into perspective the results obtained by other diagnostic methods. Because the study of biofilms and implant-associated infections is a relatively new field of research, many questions remain regarding the pathogenesis and in vivo colonization used by various species of bacteria in biofilms. A better understanding of these essential aspects of biofilm-related infections at the molecular level, including specific virulence factors like genes, will help define the appropriate targets for therapeutic interventions, improve diagnosis and to develop new antibiofilm materials. In the context of the rapid development of new state of the art molecular diagnostic methods, DNA sequencing, mass spectroscopy-based proteomics, and metabolomics, it is possible to study the details of infections in vivo. The resulting knowledge definitely and undoubtedly will contribute to the understanding of new objectives in the fight against pathogens capable of developing biofilms, in the case of infections associated with the presence of implants.

4. PERIPROTHETIC JOINT INFECTIONS.

4.1. Introduction

Over 65% of infections are biofilm-related infections (10). Every year, more than 12 million cases of biofilm-related infections (BRI) are reported in the United States, of which the most common are the ones associated with orthopedic implants (11). The surface of the most used orthopedic implants is made of titanium (or titanium alloy), stainless steel, cobalt-chromium, various polymeric biomaterials (ceramic, hydroxyapatite, or polyethylene), and polymethylmethacrylate (PMMA) cement which are structures susceptible to colonization and therefore the formation of bacterial biofilm (82) (10).

The first hip arthroplasty was performed by Smith-Petersen in 1939. This was a partial arthroplasty with a cup of vitallium and was considered a breakthrough in the treatment of osteoarthritis (83). However, a few years later, their initial enthusiasm declined as complications such as periprosthetic joint infection were observed (84). During the same period, Elek and Conen (85) reported the consequence of the presence of a foreign body on the virulence of *Staphylococcus aureus*, which increases at least by 10,000 times. The reason for the inadequate clearance of microorganisms adhering to the foreign material is the consequence of the altered functioning of the granulocytes that surround the endoprosthetic implant (86) (87). In addition to this high susceptibility to infections, antimicrobial therapy has a limited efficacy on microorganisms that grow as biofilms, a tolerance that increases with the age of the biofilm (88) (89). Therefore, a quick and correct diagnosis of the infection associated with an orthopedic implant but not only is mandatory to try to save the implant.

4.2. Definition and classifications

Surgical site infections (SSIs) are generally classified according to CDC definitions (90). This classification divides SSIs into superficial infections - incisional, deep, and organ/space. Periprosthetic joint infections correspond to an SSI of the organ/space. However, there is no clinical, laboratory, or imaging procedure that can reliably differentiate between these different types of infections. According to Berbari et al. (91), superficial SSIs represent the highest risk factor for periprosthetic joint infections (OR 35.9, 95% CI 8.3-154.6). The progression from a superficial SSI to an organ/space one is very frequent and clinically, unfortunately, unpredictable. Table 5 presents the criteria for defining cases of periprosthetic joint infections, criteria according to the IDSA-Infectious Disease Society of America and the MSIS-Musculoskeletal Infection Society.

Traditionally, periprosthetic joint infections are classified as early (<3 months), delayed (3-24 months), and late (> 2 years after implantation), unfortunately, a classification that is not clinically useful. Therefore, there is a classification that dictates the optimal surgical management of periprosthetic joint infection (92). Acute hematogenous periprosthetic joint infection lasting no more than 3 weeks after a postoperative period without complications. Early postoperative

periprosthetic joint infections are defined as infections that occur within one month after an invasive procedure, such as arthroplasty or arthrocentesis. Chronic periprosthetic joint infection is either a hematogenous infection with symptoms that persist for >3 weeks, or an infection diagnosed >1 month after surgery. Acute hematogenous or early postoperative periprosthetic joint infections can be successfully treated with implant retention. In contrast, in patients with chronic periprosthetic joint infection, the chance of removing the biofilm from the implant surface is less than 50%, even in the context of prolonged antimicrobial therapy.

Table 1 Definition criteria of periprosthetic joint infections acordint to the IDSA and MSIS criteria

IDSA (For the diagnosis of PJI at least one of the five criteria is required) (93): • Presence of a sinus tract communicating with the prosthetic joint • Presence of purulence without another known aetiology surrounding the prosthetic device • Acute inflammation consistent with infection at histopathological examination of periprosthetic tissue • Elevated leucocyte count in the synovial fluid and/or predominance of neutrophils (94) (95) • Growth of identical microorganism in at least two intraoperative cultures or combination of preoperative aspiration and intraoperative cultures in case of a low-virulence microorganism (coagulase-negative staphylococci, *Propionibacterium acnes* etc.). In case of a virulent microorganism (e.g. *Staphylococcus aureus*, *Escherichia coli* etc.), growth in a single specimen from synovial fluid and/or periprosthetic tissue and/or sonication fluid may also represent PJI. However, growth in a single specimen must always consider other criteria and constellation of diagnostic procedure (e.g. previous antimicrobial treatment) in account.
MSIS (For the diagnosis of PJI, at least one major or four minor criteria must be met) (96) (97): Major criteria • Presence of a sinus tract communicating with the prosthetic joint • A pathogen is isolated by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint Minor criteria (a) Elevated ESR (>30 mm/h) and CRP (>10 mg/L) (b) Elevated synovial fluid leucocyte count (>3000 cell/uL) (c) Elevated synovial fluid neutrophil percentage (>65%) (d) Presence of purulence in the affected joint (e) Isolation of a microorganism in one periprosthetic tissue or fluid culture (f) >5 neutrophils per high-powered field in five high-power fields observed from histologic tissue at x400 magnification

PJI, Periprosthetic joint infection; IDSA, Infectious Disease Society of America; MSIS, Musculoskeletal Infection Society; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein.

The year 2011 represents the key point of standardization of the management of the periprosthetic joint infections, the year in which took place the First International Consensus Meeting on Musculoskeletal Infections in Philadelphia.

In 2018, the 2nd International Consensus Meeting on Musculoskeletal Infections (ICM) takes place, which proposes a new set of criteria for the diagnosis of periprosthetic joint infections, criteria that are based on the old consensus criteria.

Perhaps the easiest way to use to diagnose and classify a periprosthetic joint infection is the Pocket Guide for the Diagnosis and Treatment of Periprosthetic Joint Infections created by the PRO-IMPLANT Foundation, Berlin, Germany (coordinated by N. Renz and A. Trampuz) - Pocket Guide to Diagnosis & Treatment of Periprosthetic Joint Infection (PJI), a guide that is in accordance with national and international recommendations, and also updated regularly.

4.3 Clinical picture

From the point of view of the clinical picture, there are two types of manifestations of infections: acute and oliogosymptomatic. Acute manifestations are: fever and chills (caused by bacteremia), acute inflammation cardinal signs, joint swelling, or active fistula/ sinus tract. When the source of the infection is a hematogenous one, initially the systemic manifestations can predominate and later the local ones as in the case of endocarditis, pneumonia, or urinary tract sepsis. Oligosymptomatic infections are more difficult to differentiate from aseptic loosening or exceeding the life of the endoprosthetic implant, being characterized by chronic pain, subfebrile, swollen joints, and radiological signs of loosening.

4.4 Microbiology

Table 11 summarizes the etiological agents involved in periprosthetic joint infections in a group of 618 patients that underwent a total hip or knee arthroplasty procedure (92). In two recent cohort studies, the rate of patients with periprosthetic joint infection caused by Gram-negative bacilli was higher, respectively 42% (63/152) and 28% (632/2288 (101) (102). Several factors are implicated that may lead to a selective increase in Gram-negative bacilli in patients with periprosthetic joint infections, namely: (i) the use of vancomycin in prophylaxis, (ii) decolonization procedures with mupirocin, (iii) unnecessary empirical therapy with antibiotics in the early postoperative period, and (iv) antibiotic treatment in a patient with wound healing disorders. Thus, vancomycin prophylaxis should be administered only in case of an increased prevalence of MRSA (Methicillin-resistant *Staphylococcus aureus*) (103). In patients with wound healing disorders, such as a dehiscent wound or the presence of secretions, debridement surgery is required.

4.5 Paraclinical diagnosis of the orthopedic implants associated infections - medical imaging in routine implementation

Contemporary arthroplasty interventions began 75 years ago when the predecessor of modern hip systems was for the first time introduced. A total hip arthroplasty includes both femoral and

acetabular components; a hemiarthroplasty consists only of the femoral component. These prostheses are integrated into the bone by various methods, including cementing the implant using PMMA (polymethylmethacrylate) and direct bone integration through the development of bone tissue at the surface of the endoprosthetic device. Some devices are coated with hydroxyapatite which induces bone formation and thus the attachment of the newly formed bone tissue to the prosthetic components. The acetabular component can be stabilized at the acetabulum with or without screws (stabilization called press-fit) (104). Regarding the knee prostheses, their history begins about 40 years ago. They consist of a femoral and tibial metal component, a crosslinked polyethylene insert/liner as well as a polyethylene patella endoprosthesis component. Current knee implants show a significant improvement in the degree of mobility as well as the increased durability of the components. Currently, the most common cause of revision of an endoprosthesis is aseptic loosening, which occurs in a quarter of cases from a reactive inflammatory process to the presence of endoprosthetic components. Particles resulting from the degradation of prosthetic components ("free bodies") attract and activate leukocytes in the periprosthetic tissues, activating the secretion of cytokines and enzymes that lead to periprosthetic bone tissue degradation - aseptic loosening (104).

The diagnosis of orthopedic implants associated infections is based on a combination of clinical signs, laboratory, data and imaging studies. There is no "gold standard" imaging technique: conventional radiography is indispensable, although in 50% of cases the radiography is unchanged. Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography are valuable for detecting soft tissue abnormalities. Bone scintigraphy excludes an active infection. For infections involving the peripheral skeleton, labeled leukocyte scintigraphy associated with colloidal scintigraphy is the reference technique, while gallium scintigraphy is always required for imaging of the spine or pelvis. To confirm or rule out infections, arthrocentesis with analysis of the synovial fluid is the key to the diagnostic algorithm.

4.8 Paraclinical diagnosis of the orthopedic implants associated infections - laboratory diagnosis

Among the laboratory changes, an ESR over 30mm/h or a CRP (C-reactive protein) over 10mg/L is suggestive for acute infection with a sensitivity of 91-97%, a specificity of 70-80%, and a negative predictive value of 96 %, while in the case of chronic infections (associated with a mature biofilm) the usefulness of these markers decreases greatly. The American Consensus warns against these values due to the differences between the laboratories in which these analyzes are performed, and the changes depending on the patient's age, gender and comorbidities; at the same time, it warns of the possibility of these markers being raised to 60 days after primary or previous surgery (98).

Examination of synovial fluid in case of a periprosthetic joint infection may reveal the following changes: leukocytes over 4200/uL or over 80% polymorphonuclear granulocytes in the case of hip prostheses, and the case of knee implants, leukocytes over 1700/uL or over 65% polymorphonuclear granulocytes - values which can be applied in case of a maximum interval of 2 months postoperatively; beyond this range, leukocyte values above 25000/uL are required (139).

Classical diagnostic methods, such as cultures, often do not show the presence of a pathogen agent (a sensitivity between 13.4% and 94.8%) depending on the number of samples - preferably collecting at least 3 specimens, but no more than 5 (98).

According to the European guidelines for the diagnosis and treatment of biofilm-related infections, published in 2014 (33), highlighting of the biofilm can be done either by electron microscopy or by FISH (Fluorescence in situ hybridization) techniques with a sensitivity between 80 % -100% (10), techniques associated or not with PCR detection methods.

Among the microscopic techniques for highlighting the biofilm, optical microscopy associated with a Gram stain can be used, which highlights the inflammatory cells, bacteria, and the biofilm matrix (AII) (32). Techniques such as confocal laser scanning microscopy (CLSM) and electron microscopy (SEM scanning electron microscopy) are the best methods for highlighting biofilm, having the disadvantage of not being able to be performed in a routine manner (BIII) (35).

In addition to these previously mentioned techniques, the use of sonication, a relatively cheap method, significantly increases the diagnosis rate (36). Following sonication, the number of colony-forming units (CFUs) can also be reported (33). The orthopedic implants are placed in a sonication bath that produces air microbubbles, which produce enough energy to detach the biofilm from the implant surface, after which this fluid can be cultured on different culture media or analyzed with FISH techniques (AII) or PCR techniques can be applied (37) (38).

Studies such as those of Bouza et al. and Percival et al, demonstrated that by sonication or centrifugation more colony-forming units of *Candida* spp. are recovered than after brazing/scarping (140) (141).

In Romania, since 2012, sonication has been used in the National Institute of Infectious Diseases "Prof. Dr. Matei Bals"; the only published data are from July 2012 to July 2014, a study that included 39 orthopedic implants (21 hip prostheses, 11 knee prostheses, and 7 fixation devices) (142).

The histopathological diagnosis criteria are very different; there is a consensus that the presence of more than 5 neutrophils/microscopic field (400x) in 5 different areas represents an important suspicion of an infection.

Non-specific proinflammatory markers, such as C-reactive protein, procalcitonin, erythrocyte sedimentation rate, leukocytes, or various cytokines, cannot distinguish between infections caused by planktonic bacteria and biofilm (DIII).

4.9 Therapeutic management

The first question is whether the purpose of treatment is to cure or suppress the infection. The goal of any treatment should be healing/cure, and suppression should be the exception, as it is only a palliative procedure. We can define healing/cure as the elimination of all microorganisms and the preservation or restoration of a good joint range of movements. The success of the treatment

was recently defined; in short, it includes eradication of the infection in the context of a completely healed wound, lack of recurrence without the need for further surgery to eradicate the infection after reimplantation, and absence of mortality related to periprosthetic joint infection up to 2 years after definitive surgery associated with the periprosthetic joint infection (150). A therapeutic option for the management of periprosthetic joint infection targeting treatment requires a multidisciplinary case discussion, including at least one orthopedic surgeon and a specialist in infectious diseases. In complex cases, this group should include a clinical microbiologist and a plastic-reconstructive surgeon. In the case of patients with comorbidities or in the case of those who cannot ambulate, it may be reasonable to choose a palliative strategy. The same is true for patients at high risk of reinfection, such as people that actively are using intravenous drugs (151).

Biofilm-related orthopedic implant infections can be prevented by the use of perioperative antibioprophylaxis (AI) (Song, et al., 2013).

There are clear studies that have shown that the use of antibiotic-impregnated materials, such as cement (frequently gentamicin but also tobramycin or vancomycin), reduces the rate of biofilm-associated prosthetic joint infections (AI) (Parvizi, et al., 2008) (Marschall, et al., 2013).

The management of periprosthetic joint infections consists of antibiotic therapy both generally and locally, associated with surgery. There are mainly 7 treatment methods: debridement and implant retention of the implant (DAIR), one-step revision, two-steps revision, implant removal, arthrodesis, suppressive antibiotic therapy, and the final option - amputation (Domizia, 2015).

4.10 Conclusions

The diagnosis and management of prosthetic joint infections remain an issue. Prosthetic joint infections remain the most feared complications associated with arthroplasty interventions. Despite scientific progress in recent years, the incidence of infections is increasing, both related to the increase in the number of primary interventions and the emergence of multidrug-resistant microorganisms. There are a lot of unanswered questions. Is it recommended to use systemic antibiotics or only local ones? Can we trust bacterial cultures for bacteria that grow in colonies? Or associate sonication on a regular basis? Should vascularization of the remaining bone be sacrificed after removal of the infected implant? because we know that biofilm develops on surfaces. The existence of the 3-week “window” is a key time point in which we either won the battle for the “surface” or lost it. Is long-term antibiotic therapy necessary? If we managed to perfume a good debridement and remove the affected tissues from the site, why not perform the revision in the same surgery? The existence of protocols adapted to the treatment of biofilm-related infections and new diagnostic methods has improved the rate of eradication of infections, without having 100% certainty that we have eradicated the infection. Well-equipped treatment centers for diagnosis and multidisciplinary surgeon-ID specialist-microbiologist teams are needed.

Currently, nuclear medicine is the most valuable investigation that can determine whether or not it is a "painful" septic arthroplasty. Leukocyte scintigraphy and bone marrow imaging are

currently the best imaging technique available for this purpose. Preliminary data suggest that SPECT/CT, in addition to providing information on the presence and extent of the infection, may provide additional information on other causes that may cause arthroplasty to fail. Fluoride-PET may provide a hitherto unknown perspective related to periprosthetic bone tissue metabolism.

PERSONAL CONTRIBUTION

1. THE MOTIVATION OF CHOOSING THE RESEARCH TOPIC.

Orthopedic surgeries for total joint arthroplasties, especially of the hip and knee, along with that of the shoulder or elbow to a much lesser extent, are the most successful orthopedic surgeries of the last century, with the primary goal of regaining the activity of people affected by osteoarthritis but not only (since endoprosthetic implants are used more and more frequently in the elderly population, a population that is growing, especially for the management of degenerative pathology but also of fractures). Total joint replacement interventions have a major effect on people's quality of life, they reduce symptoms, regain joint function, improve mobility and independence (229). The number of arthroplasty interventions is increasing from year to year, so in 2010 in the United States were performed 719,000 interventions of total hip arthroplasties (230) and in 2012 were performed approximately 600,000 total knee arthroplasties (231). By 2030, the combined annual number of total knee and hip arthroplasties in the United States is expected to reach 3.5-4 million.

Thus, with the increase in the number of primary and revision interventions, it is obvious the presence of orthopedic implants associated infections, infections that appear despite hospital conditions of asepsis and antisepsis, implant production conditions, or prophylactic therapy with antibiotics, all these measures intend to reduce the rate of infection. The rate of infections associated with prosthetic implants is between 1% - 9% with its increase following revision interventions. It is considered that between 0.5% - 2% of patients develop a biofilm-related infection associated with an orthopedic implant in the first 2 years postoperatively (232) (233) (234).

A correct and rapid diagnosis of periprosthetic infections is crucial for proper therapeutic management. The diagnosis is based on a combination of clinical signs, laboratory data, and imaging studies, however, this diagnosis remains difficult. Periprosthetic joint infections are also associated with an increased length of hospitalization as well as high treatment costs. The therapeutic management of cases of aseptic loosening of the endoprosthesis is different from that of periprosthetic joint infections, and an accurate diagnosis is crucial for the outcome of treatment.

In this context, I decided to conduct scientific research entitled: "Diagnosis and Management of orthopedic implants biofilm-related infections.", by which I intend to study the true magnitude of orthopedic implants biofilm-related infections (especially joint arthroplasty implants - endoprosthetic implants for the hip and knee) and the implementation of diagnostic and therapeutic management strategies.

3. MATERIAL AND METHOD.

Study design

I conducted a monocentric, observational, cohort study at the Academic Emergency Hospital Sibiu, Romania, a county hospital with 1054 beds. The study protocol was evaluated and approved by the institutional evaluation committee before the patients were included in the study. A standardized diagnostic system was applied to all patients who were candidates for a surgical intervention of joint arthroplasty revision to determine the cause of endoprosthetic loosening. The implemented diagnostic strategy included a standardized sampling of at least four tissue samples harvested intraoperatively (one of the samples being used for histopathological examination (periprosthetic membrane) and the others were sent to the microbiology laboratory for bacterial cultures), sonication of endoprosthetic implant components removed or polymethylmethacrylate (PMMA) spacers and sonication fluid harvesting, bacterial cultures and evaluation of synovial fluid cellularity, detection of leukocyte esterase and C-reactive protein in synovial fluid and evaluation of sonication fluid using a bbFISH assay (hemoFISH® Masterpanel, Miacom diagnostics GmbH Düsseldorf, Germany) as a rapid method for the detection of bacteria. The specimens were inoculated on aerobic and anaerobic culture media. A 14-day incubation period was also implemented for all cultures.

The sonication of the implant was performed in the laboratories of the Biochemistry Department within the “Lucian Blaga” University of Sibiu - Faculty of Medicine following the establishment of a collaboration protocol.

The microbiology studies were carried out by involving, since the beginning of the study, the senior management of the European Hospital Polisano Sibiu and especially its laboratory staff.

Study population

I included, in a prospective manner, all consecutive patients over the age of 18 years old, hospitalized between September 2016 and January 2019, patients who underwent a surgical procedure of joint revision arthroplasty (either hip or knee), in which the prosthesis or part of it (such as the liner) was removed for any reason. Also included in the study were the interventions that involved the removal of a polymethylmethacrylate spacer. Detailed information was extracted from patients' medical records using a standardized digital data collection form. Medical records were evaluated in this study for the following data: demographic characteristics; clinical, radiographic, laboratory, histopathological, and microbiological data; type of surgical treatment; previous antimicrobial therapy and information on primary arthroplasty and subsequent revisions (if any). The necessary information was available for all patients enrolled in the study. The patients were followed until they developed a treatment failure, died, or were lost during the follow-up period. The follow-up period was extended until January 2020, so the patients were followed for a maximum period of 39 months.

The collected data were processed in Microsoft Excel 2020, and subsequently statistically analyzed using IBM SPSS Statistics® version 26 software. The collected data were analyzed and verified using the Shapiro-Wilk test. Descriptive statistics were used to summarize demographic, clinical, and treatment aspects. Quantitative variables were expressed as mean ± SD (standard deviation) or a median. The qualitative variables were summarized numerically and in percentage. Quantitative variables were compared using Student`s t-test or Chi-Square test. The Kruskal-Wallis test, the Kaplan-Meier analysis for survival rate, the ROC curve (Receiver operating characteristic) for the sensitivity and specificity of the different diagnostic methods analyzed, and the Cox multivariable analysis were also used. The two groups of patients were compared using the incidence frequency (%), Chi-Square Tests, the Fisher's exact test, the Pearson P-R correlation coefficient, and bivariate correlation. The significance of the differences between the 2 study groups was analyzed using the Mann – Whitney U test for non-parametric one-tailed significance. Regression analysis was also used, through multivariate analysis models - analytical models for obtaining regression equations, coefficients of regression models. By analyzing the regressions, it was intended to identify the links between the analyzed variables; through successive commands Analyze → Regression → Curve Estimation → Curve Estimation window, the types of multivariate analysis models were selected - analytical models for obtaining regression equations. The odds ratio and 95% CI (confidence intervals) were calculated for each of the risk factors included in the logistic regression models. The level of statistical significance was set at $p < 0.05$.

Study definitions and classifications

Periprosthetic joint infections were defined using the criteria published in 2011, which was the key point for standardizing the management of periprosthetic joint infections, and the year in which the First International Consensus on Musculoskeletal Infections in Philadelphia took place and the criteria of the working group within the Musculoskeletal Infection Society published by Javad Parvizi et al . were elaborated: (i) a sinus tract communicating with the prosthetic joint; (ii) A pathogen that is isolated by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint; or (iii) the existence of at least four of the following six criteria: an increased erythrocyte sedimentation rate (ESR) and an elevated serum C-reactive protein (CRP) level; an increased number of leukocytes in the synovial fluid; an increased percentage of neutrophils in synovial fluid (PMN%); the presence of pus around the involved joint; isolation of a microorganism in one periprosthetic tissue or fluid culture or fluid or more than five neutrophils per microscopic field (high-power microscopic field) observed during histological analysis of periprosthetic tissue at a magnification of × 400 (96)

To determine whether or not there is an acute, chronic, or late-acute periprosthetic joint infection, the classification proposed by Zimmerli et al. was used, a classification that defines periprosthetic joint infections as early (occurring within 3 months postoperatively), delayed (3 -24 months) and late (> 24 months) (236). Also used was a much simpler classification from the Pocket Guide for the Diagnosis and Treatment of Periprosthetic Joint Infections created by the PRO-IMPLANT Foundation, Berlin, Germany (coordinated by N. Renz and A. Trampuz) - Pocket Guide to Diagnosis & Treatment of Periprosthetic Joint Infection (PJI), a guide that is in line with

national and international recommendations – PJIs can be acute (perioperative or hematogenous/continuous) or chronic.

Histopathological classification of the pathology associated with joint implants

From the intraoperative samples of periprosthetic tissue (periprosthetic membrane), one of them was sent to the Department of Pathological Anatomy.

Synovial fluid cultures

Synovial fluid was aspirated preoperatively under aseptic conditions. The aspirate was subsequently transferred into two sterile vacutainer vials. One of the vials contains EDTA (ethylenediaminetetraacetic acid) and was used to determine the number of leukocytes and the percentage of granulocytes. The other was a native vial used for bacterial culture. The synovial fluid was inoculated and incubated under aerobic, anaerobic, and high CO_2 conditions at 37°C for 14 days and inspected daily for bacterial growth. Isolated bacteria were identified using the VITEK 2 Compact analyzer (bioMérieux, Marcy-l'Étoile, France). MICs (minimum inhibitory concentrations) were assessed in accordance with the European Committee on Antimicrobial Susceptibility Testing breakpoints (EUCAST) (94) (93).

Implant sonication and sonication fluid cultures

Both endoprosthesis and polymethylmethacrylate spacers were retrieved and sonicated. In the operating room, sterile Ringer's solution or 0.9% NaCl saline (saline sterile solution) was added into the sterile containers designated for implant sonication. The above containers are sterilized according to the manufacturer's recommendations and packed in a double layer envelope. The implants were processed within 30 minutes by sonication (1 min) using an ultrasonic bath (BactoSonic®14.2, Bandelin GmbH, Berlin, Germany) at a frequency of 42 kHz and a power density of 0.22W/cm^2. The resulting sonication fluid was vortexed and subsequently, 50 ml of sonication fluid were centrifuged at 2500 rpm for 5 minutes. The resulting precipitate was inoculated on culture media: Columbia agar with sheep blood (incubated aerobically, anaerobically, and in high CO_2 concentration - GENbag-GENbox Atmospheric generators bioMérieux, Marcy-l'Étoile, France), Sabouraud plate, plate MacConkey agar, glucose broth, lactose broth, and thioglycolate broth.

The cultures were incubated at 37°C for 14 days and inspected daily for bacterial growth. Isolated bacteria were identified using the VITEK 2 Compact analyzer (bioMérieux, Marcy-l'Étoile, France). The MICs were evaluated according to EUCAST breakpoints. Sonication fluid cultures were considered positive if >50 CFU/ml (CFU – colony-forming units) of sonication fluid were counted (52) (162).

Periprosthetic tissue cultures

Biopsy samples of periprosthetic tissue of approximately 1.5 cm^3 in size were sampled intraoperatively and collected in sterile vials, transported as soon as possible to the microbiology laboratory where they were individually homogenized in one ml of thioglycolate broth. Homogenized tissue samples (1 ml) were inoculated on culture media as follows: Columbia agar with sheep blood (incubated aerobically, anaerobically, and in high CO_2 concentration - GENbag-GENbox Atmospheric generators bioMérieux, Marcy-l'Étoile, France), Sabouraud plate, MacConkey agar plate, glucose broth, lactose , and thioglycolate broth. The cultures were incubated at 37°C for 14 days and inspected daily. Isolated bacteria were identified using the VITEK 2 Compact analyzer (bioMérieux, Marcy-producétoile, France), and the MICs were evaluated according to EUCAST breakpoints.

Synovial fluid studies

Synovial fluid was analyzed for cellularity, C-reactive protein levels, and leukocyte esterase. Preoperatively synovial fluid was aspirated and transferred to sterile vials. One of the vials contained EDTA to determine the number of leukocytes and the percentage of granulocytes. After collection, the samples were transported to the laboratory, where the vials were processed within 10-15 minutes. I evaluated previous studies that established optimal levels for the diagnosis of periprosthetic joint infections, a synovial fluid leukocyte count greater than >1.7 G/l or >65% neutrophils in knee arthroplasties or leukocyte count > 4.2G/l or >80% neutrophils in hip arthroplasties (Kurtz, Ong, Lau, Mowat, & Halpern, 2007) (52). Regarding the detection of leukocyte esterase, I evaluated the synovial fluid using enzymatic colorimetric bands (Dirui A10 Urine Analysis Reagent Strips, Dirui Industrial Co. Ltd, Changchun, China). To limit interference with the assays, between 1-4 ml of synovial fluid were centrifuged at 2500 rpm for 5 minutes. A drop of the resulting precipitate was placed on the leukocyte esterase detection strip. The reaction was evaluated according to the manufacturer's recommendations. Highlighting the color purple indicated a positive test. Determination of C-reactive protein in synovial fluid was performed by an automated turbidimetric method using a specific reagent kit and, on an ARCHITECT c4000 system (Abbott Laboratories, Illinois, USA).

Molecular identification of bacteria using 16S rRNA bbFISH technology (beacon-based fluorescent in situ hybridization) from the sonication fluid

Also, as a rapid method for detecting and analyzing bacteria, I implemented a molecular identification technique for bacteria using 16S rRNA bbFISH (beacon-based fluorescent in situ hybridization) technology using a bbFISH kit (hemoFISH® Masterpanel, miacom® diagnostics GmbH Düsseldorf, Germany. Miacom® diagnostics GmbH combines the advantages of the classic FISH with the use of fluorescently labeled DNA-molecular beacons as probes, resulting in a very easy procedure. The bbFISH test was performed according to the manufacturer's recommendations, using a precipitate sample resulting from 50 ml of pre-centrifuged sonication

liquid at 2500 rpm for 5 minutes The kit contains beacons for the detection of the following bacteria: *Staphylococcus* spp., *Staphylococcus aureus*, *Streptococcus* spp., *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Enterococcus faecium*, *Enterococcus faecalis*, *Enterobacteriaceae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*.

4. RESULTS.

4.1 Demographic, clinical, and laboratory aspects. Classification of the periprosthetic joint infections.

4.1.1 Demographic aspects

A total number of 61 patients were enrolled in this study during the analyzed period (September 2016 - January 2019), representing a total number of 61 implants that were retrieved, endoprosthesis (n=58) or polymethylmethacrylate (PMMA) spacers (n=3). The diagnosis of aseptic loosening of an endoprosthetic implant was established in 30 cases (49.18%) and the diagnosis of infection associated with an endoprosthetic implant (periprosthetic joint infection) was established in 31 cases (50.81%). Thus, in 2016, 14 patients were enrolled (23%), 7 patients belonging to the study group of patients diagnosed with aseptic loosening, and 7 patients diagnosed with a prosthetic joint infection. In 2017, 19 patients were enrolled (31.1%), 13 patients belonging to the study group of patients diagnosed with aseptic loosening, and 6 patients diagnosed with periprosthetic joint infection. In 2018, 17 patients were enrolled (27.9%), 8 patients belonging to the study group of patients diagnosed with aseptic loosening and 9 patients diagnosed with a periprosthetic joint infection, and in 2019 11 patients were enrolled in the study (18%), 2 patients belonging to the study group of patients diagnosed with aseptic loosening and 9 patients diagnosed with periprosthetic joint infection. There were no statistically significant differences between the 2 study groups regarding the patient enrollment year (p=0.690).

Of the 30 retrieved implants from the 30 patients diagnosed with aseptic loosening of an endoprosthetic implant, 16 implants were hip and 14 knee implants, and in the group of patients diagnosed with a periprosthetic joint infection, 14 implants were hip implants, 14 knee implants, and 3 hip polymethylmethacrylate spacers. Regarding PMMA spacers, the initial surgeries (the first stage of a two-stage revision surgery) were performed before the introduction of the proposed diagnostic strategy and no pathogen had been isolated.

Compared to the whole study group (n = 61), the mean age of the enrolled patients was 67.62 years (range, 44 - 83 years, standard deviation ± 8.058). In the subgroup of patients diagnosed with aseptic loosening, the mean age of the enrolled patients was 68.50 years (range, 44 - 83 years, standard deviation ± 8.768). In the subgroup of patients diagnosed with a periprosthetic joint infection, the mean age of the patients was 68 years (range, 49 - 83 years, standard deviation ± 7.422).

29 patients were male patients (47.5%) and 32 patients were living in rural areas when analyzing the entire study population.

22 patients were female patients (73.33%) and 17 patients were living in rural areas (56.66%) in the subgroup of patients diagnosed with aseptic loosening and when analyzing the subgroup of patients diagnosed with a periprosthetic joint infection, 10 patients were female patients (32.25%) and 15 patients were living in rural areas (48.38%).

There were no statistically significant differences between the 2 study groups when analyzing the age or residence medium, p=0.574, respectively p=0.517. From the gender point of view, there were statistically significant differences between the 2 subgroups, p=0.001.

A not negligible parameter in the evaluation of an endoprosthetic implant is the year in which the primary endoprosthesis intervention took place, in the entire study group the interval in which the primary endoprosthesis intervention took place was between 2000 and 2019 and the duration from the time of the initial intervention and enrollment in the study was between 2 weeks and 17 years (statistical data for the whole study group, n = 61). These parameters are extremely important in terms of evaluating an implant and even more so in the case of periprosthetic joint infection. Thus, in the case of the subgroup of patients diagnosed with a periprosthetic joint infection, the primary endoprosthesis intervention took place between 2003-2019 and the duration from the time of initial intervention and the enrollment of the patients in the study was between 2 weeks and 15 years (n=31), and in the subgroup of patients diagnosed with a mechanical loosening of an endoprosthetic implant, the primary intervention took place between 2000-2016, and the duration from the initial intervention and enrollment in the study was between 1 year and 17 years (n=30). Also from this point of view of these 2 parameters, there are statistically significant differences between the 2 study subgroups, p=0.010 in the case of the period in which the primary intervention took place, respectively p=0.018 in the case of the interval between the initial intervention and enrollment in the study.

The most common underlying joint condition in the group of patients diagnosed with aseptic loosening of an endoprosthetic implant was osteoarthritis (n=22), followed by rheumatoid arthritis (n=6) and trauma - femoral neck fracture (n=2). In the group of patients diagnosed with a periprosthetic joint infection, the most common underlying joint condition was osteoarthritis (n=28), again followed by rheumatoid arthritis (n=2) and trauma - femoral neck fracture (n=1).

4.1.2 Classification of the periprosthetic joint infections.

The diagnostic criteria used in establishing the diagnosis of periprosthetic joint infection that were used were according to the guidelines of The IDSA (93), MSIS (96)(97), and those of the First International Consensus Meeting on Musculoskeletal Infections in Philadelphia from 2011 or those from 2018 from the 2nd International Consensus Meeting on Musculoskeletal Infections in Philadelphia.

Using the classification proposed by Zimmerli et al., a classification that defines periprosthetic infections as early (occurring within 3 months postoperatively), delayed (3-24 months), and late (> 24 months) (236) I was able to group the 31 patients diagnosed with periprosthetic infection as follows: 9 patients diagnosed with early periprosthetic joint infection, 6 patients with delayed periprosthetic joint infection and 16 patients diagnosed with a late periprosthetic joint infection.

I also used a much simpler classification of the periprosthetic joint infections from the Pocket Guide for the Diagnosis and Treatment of Periprosthetic Infections created by the PRO-IMPLANT Foundation, Berlin, Germany (coordinated by N. Renz and A. Trampuz) - Pocket Guide to

Diagnosis & Treatment of Periprosthetic Joint Infection (PJI); thus, 5 patients were diagnosed with an acute perioperative infection, 4 patients with acute hematogenous infection, and 22 patients with chronic prosthetic joint infection. The number of patients diagnosed with an acute periprosthetic joint infection in 2016 was 2, in 2017 1, in 2018 1, and 2 cases in 2019. Patients diagnosed with a hematogenous acute periprosthetic joint infection in 2016 were 0, in 2017 1, in 2018 0 and in 2019 2 cases, and patients diagnosed with a chronic periprosthetic joint infection in 2016 were 0 cases, in 2017 4, in 2018 8 and in 2019 5 patients.

4.1.3 Clinical aspects

In the group of patients diagnosed with a periprosthetic joint infection, the mean duration in years from the time of primary intervention until the onset of symptoms was 3.23 years (± 3.62 years) with 95%CI[1.90 - 4.55] for the mean, with a minimum of 2 weeks and a maximum of 15 years.

51.61% (n = 16) of the episodes of periprosthetic joint infection occurred more than 24 months after the primary surgical intervention.

The clinical picture, signs, and symptoms, presented by patients diagnosed with a periprosthetic joint infection, are reported in the following table.

Table 2 Signs and symptoms of the 31 enrolled patients diagnosed with prosthetic joint infections

Signs and symptoms	No. of episodes (%)
Compromised soft tissue:	
Slightly damaged soft tissuea[a]	7 (22.58)
Moderately damaged soft tissue[b]	3 (9.67)
Severely damaged soft tissu[c]	6 (19.35)
Pain	22 (70.96)
Fever	3 (9.67)
Chills	2 (6.45)
Bacteraemia	3 (9.67)
Loose implant	15 (48.38)

a: erythema and induration; b: wounds without discharge; c: wound discharge, sinus tract, and abscess.

The presence of a fistula was evidenced in 6 patients diagnosed with a periprosthetic joint infection.

4.1.4 Laboratory aspect

4.1.4.1 Synovial fluid studies

Synovial fluid was analyzed for cellularity, C-reactive protein levels, and leukocyte esterase.

The performances of the diagnostic methods used in the evaluation of synovial fluid are summarized in the following table.

Studying the level of C-reactive protein in synovial fluid reported the best performance in terms of sensitivity, followed by leukocyte count, polymorphonuclear percentage, and leukocyte esterase.

In terms of specificity, the highest specificity was found in determining the number of leukocytes, followed by leukocyte esterase, the percentage of polymorphonuclear, and lastly the level of the C-reactive protein in synovial fluid.

Table 3 Performance of used diagnostic methods in the study of the synovial fluid

Diagnostic method	% sensibility (95% CI)	% specificity (95% CI)	% PPV (95% CI)	% NPV (95% CI)
Leukocyte count in the synovial fluid	90.32% (74.25%-97.96%)	100.00% (88.43-100.00)	100.00%	99.99% (99.97-100.00)
Percentage of polymorphonuclear in the synovial fluid	90.32% (74.25-97.96)	83.33% (65.28-94.36)	5.19% (2.38-10.94)	99.88% (99.65-99.96)
Percentage of polymorphonuclear	83.87% (66.27-94.55%)	90.00% (73.47-97.89%)	7.81% (2.78-20.04)	99.82% (99.59-99.92)
C-reactive protein from the synovial fluid	100.00% (88.87-100.00)	70.00% (50.60-85.27)	3.26% (1.91-5.50)	100.00%

*PPV – Positive predictive value, NPV- Negative predictive value

4.1.4.2 Study of the blood parameters of the enrolled patients

Among the laboratory performed tests and the parameters that were evaluated preoperatively in the case of a joint arthroplasty revision surgery introduced in the study are the following: the number of WBCs, fibrinogen, erythrocyte sedimentation rate (ESR), and serum C-reactive protein. It was also attempted to collect laboratory parameters related to primary surgery (proinflammatory biomarker level, pre, and postoperative hemoglobin, or serum glucose), parameters for which it was not possible to collect data related to all patients, so a detailed analysis was not performed. The existence of a possible correlation between these parameters and the subsequent development of a periprosthetic infection was evaluated, a correlation between these two parameters was not demonstrated.

The following table summarizes all demographic, clinical, and laboratory aspects of the patients enrolled in the study.

Table 4 Baseline Characteristics Table of the enrolled patients in the study

Evaluated parameter	Patients diagnosed with aseptic loosening (n=30)	Patients diagnosed with prosthetic joint infections (n=31)	*p*
Demographic data			
Type of implants	16 hip implants 14 knee implants	14 hip implants 14 knee implants 3 PMMA hip spacers	-
Age (mean, std. dev., interval) years	68,50 years (±8.768, 44 - 83).	68 years (±7.422, 49 - 83).	0.574
Gender (male, n=, %)*	8 (26.67%)	20 (67.77%)	0.001
Residence (U, n=, %)	13 (43.33%)	16 (51.62%)	0.517
Primary surgical intervention period*	2000-2016	2003-2019	0.001
Duration from the time of the initial intervention and enrollment in the study *	Between 1 year and 17 years	Between 2 weeks and 15 years	0.018

Underlying joint conditions			
Osteoarthritis (n=)	22	28	-
Connective tissues disorders**	6	2	-
Trauma***	2	1	-
Clinical aspects			
Mean duration in years from the time of the initial intervention until the onset of the symptoms (mean, std. dev., interval) years	6.76 years (± 3.57), 1 - 17 years.	3.23 years (± 3.62), 2 weeks - 15 years.	-
Surgical hip approach (n=)	lateral approach (n=16)	Lateral approach (n=16) antero-lateral minimal invasive (n=1)	0.656
Surgical knee approach (n=)	medial parapatellar (n=12) lateral parapatellar (n=1) mid-vastus approach (n=1)	medial parapatellar (n=9) lateral parapatellar (n=4) mid-vastus (n=1).	
Signs and symptoms (n=, %)			
Compromised soft tissue: Slightly damaged soft tissue[a] Moderately damaged soft tissue[b] Severely damaged soft tissu[c]	-	7 (22.58%) 3 (9.67%) 6 (19.35)	-
Pain	30 (100%)	22 (70.96)	-
Fever	-	3 (9.67)	-
Chills	-	2 (6.45)	-
Bacteremia	-	3 (9.67)	-

Loose implant	23 (76.66%)	15 (48.38)	-
Laboratory studies			
Synovial fluid studies			
Number of leucocytes (mean, std. dev., interval) G/l*	645.27 (±502.53), 180.00 - 2000.00	8962.58 (±9488.41), 300.00 G/l - 33000.00 G/l	0.000
Percentage of polymorphonuclear (mean, std. dev., interval) (%)*	52% (±16.270, 20% - 80%	82.29% (±13.00), 40% - 95%	0.000
Leukocyte esterase.* (n=, positive)	3	26	0.000
C-reactive protein (R.V. 0-0.9 mg/L) (mean, std. dev., interval)*	0.95 mg/L (±3.36), 0.00 – 18.00 mg/L	24.13 mg/L (±56.35), 0.50 – 312 mg/L	0.028
Studiul parametrilor biologici sangvini			
WBCs (R.V. 4000-9000/µl) (mean, std. dev., interval)	7944/µl (±1732), 5480 – 13490/µl	8617/µl (±1998), 4960 - 14220/µl	0.303
ESR (<20 mm/h) (mean, std. dev., interval)	23 mm/h (±13), 7 – 75 mm/h	34 mm/h (±19), 10 – 86 mm/h	0.170
Fibrinogen mg/dL (R.V. 200-400 mg/dL) (mean, std. dev., interval)*	405 mg/dL (±86), 250 – 705 mg/dL	466 mm/h (±106), 261 – 505 mg/dL	0.017
C-reactive protein (V.R. <6 mg/L)*	9.7 mg/L (±7.98), 3 – 46 mg/L	36.64 mg/L (±43.85), 3- 210 mg /dl	0.003

* - statistically significant difference between the 2 study groups; PMMA-polymethylmethacrylate; std. dev. –standard deviation; U – urban;** - rheumatoid arthritis, *** - femoral neck fracture, [a] a: erythema and induration; b: wounds without discharge; c: wound discharge, sinus tract, and abscess; R.V. – reference value, ESR – erythrocytes sedimentation rate,

4.2 Histopathological classification of the periprosthetic tissue pathology

Table 5 Histopathological evaluation of the periprosthetic membrane

	Number of cases	p=

Type of classification according to Krenn and Morawietz	Patients with periprosthetic joint infection.	Patients with aseptic loosening of the implants.	
Type I	4	10	0.59
Type II	7	0	0.005
Type III	18	11	0.097
Type IV	2	9	0.016

4.3 Considerations on the etiological aspects

Of the 31 patients diagnosed with periprosthetic joint infections, a microbiological diagnosis was obtained in 29 of the 31 cases (93.54%): 7 cases in 2016 (100%), 6 cases in 2017 (100%), 9 (100%) in 2018, and 7 cases (77.77%) in 2019. The proportion of cases with microbiological diagnosis varied significantly during the study period (p=0.00) applying a t-Test: Two-Sample Assuming Unequal Variances preceding being applied an F-test Test Two-Sample for Variances. Statistically significant variation most likely is in the context of the small number of patients enrolled in the study.

In total, 12.9% (4 cases) of the total episodes of periprosthetic joint infections were polymicrobial infections. At the same time, no significant trends were identified overtime in the increase of the number of polymicrobial infections. Thus, in 2016, 2 cases of polymicrobial periprosthetic joint infections were diagnosed and one case in 2017 and 2018, respectively. All cases of polymicrobial infections were associated with endoprosthetic hip implants.

Tabel 6 Polymicrobial infections – distribution by years and etiological agents

Year	Bacterial association
2016	*Staphylococcus aureus meticilino-rezistent* (MLSBi -inducible resistance to clindamycin strains) + *Enterobacter cloacae*
	Staphylococcus epidermidis + *Pseudomonas fluorescens*
2017	*Ralstonia pickettii* + *Pseudomonas aeruginosa*
2018	*Staphylococcus xylosus* + *Acientobacter* spp.

Table 25 summarizes the etiological agents involved in the etiology of the periprosthetic joint infections during the study period. Gram-positive aerobic cocci were the most common group of microorganisms involved in the etiology of the periprosthetic joint infections - 20 positive cultures representing 57.14%, followed by Gram-negative aerobic bacilli - 13 cultures, representing

37.14%. In 2 cases of periprosthetic joint infections from cultures, no pathogens were identified by any of the detection methods that were used in this study. The most common isolated Gram-positive cocci were coagulase-negative staphylococci (n=10) followed by *Staphylococcus aureus* (n=7), *Enterococcus* spp. (n=2) and D group *Streptococcus* (n=1). Among the coagulase-negative staphylococci, *Staphylococcus epidermidis* was most frequently isolated (n=7).

Table 7 Microbiological results of the bacterial cultures

Microorganism or group	Total no. of positive cultures (%)
Gram-positive aerobic cocci	20 (57.14%)
CNS - Coagulase-negative *staphylococci*	10 (28.57%)
Staphylococcus epidermidis	7 (20%)
Staphylococcus lentus	2 (5.71%)
Staphylococcus xylosus	1 (2.85%)
Staphylococcus aureus	7 (20%)
Methicillin-resistant *S. aureus*	6 (17.14%)
Methicillin-susceptible *S. aureus*	1 (2.85%)
Streptococcus species	1 (2.85%)
Streptococcus group D	1 (2.85%)
Enterococcus species	2 (5.71%)
Enterococcus faecalis	2 (5.71%)
Gram-negative aerobic bacilli	13 (37.14%)
Enterobacteriaceae	5 (14.28%)
Escherichia coli	1 (2.85%)
Enterobacter spp.	3 (8.57%)
Enterobacter cloacae complex	2 (5.71%)
Enterobacter amnigenus 2	1 (2.85%)
Klebsiella spp.	1 (2.85%)
Gram-negative nonfermenting bacilli	8 (22.85%)
Pseudomonas spp.	3 (8.57%)
Pseudomonas fluorescens	1 (2.85%)
Pseudomonas aeruginosa	2 (5.71%)
Acinetobacter spp.	1 (2.85%)
Ralstonia pickettii	4 (11.42%)
Without bacterial growth	2 (5.71%)

No significant linear upward or decreasing trend in the number of periprosthetic joint infections caused by Gram-negative aerobic bacilli (p=0.32) or Gram-positive aerobic cocci (p=0.06) was observed during the study period.

4.5 Molecular identification of bacteria using 16S rRNA bbFISH (beacon-based fluorescent in situ hybridization) technology from the sonication fluid

The use of molecular biology techniques to identify bacteria from the sonication fluid and thus the etiology of the prosthetic joint infections in patients enrolled in the study was the second main objective of this research study.

The use of 16S rRNA bbFISH (beacon-based fluorescent in situ hybridization) technology on sonication fluid samples using a bbFISH kit (hemoFISH® Masterpanel, miacom® diagnostics GmbH Düsseldorf, Germany) with a sample processing time of 30 minutes and having a possible etiological orientation, in accordance with the types of bacteria that can be identified with this kit, fast, from the day of the intervention, with the possibility of adapting the empirical antibiotic therapy centered on a certain species of bacteria. A total of 61 sonication fluid samples, representing the 61 patients enrolled in the study, were analyzed using the rapid molecular bacteria detection assay. 26 samples were positive on microscopic examination, thus identifying 26 bacteria involved in the etiology of periprosthetic joint infections, identification in accordance with the types of bacteria that can be detected using the hemoFISH® Masterpanel kit. In addition to the actual identification, the microscopic evaluation also revealed in situ information about cell morphology, number, the spatial distribution of the microorganisms, and data regarding the cellular environment around the bacteria. Thus, all strains of *Ralstonia pickettii* (n=4) were not identified in the context in which the diagnostic kit does not contain beacons for the identification of these bacterial species. Also, the *Pseudomonas fluorescens* strain was not identified, although the kit contains beacons for the detection of bacterial species of *Pseudomonas aeruginosa* type, no cross-reactions are possible, these beacons being specific to a single bacterial type.

Table 8 Bacterial identification using the 16S rRNA bbFISH technology

Bacterial strains identified from the sonication fluid cultures	Bacterial identification using the 16S rRNA bbFISH® technology	No. of identified strains	Comments
Methicillin-resistant *Staphylococcus aureus* (MLSBi -inducible resistance to clindamycin strains)	*Staphylococcus aureus*	5	
Methicillin-susceptible *S. aureus*	*Staphylococcus aureus*	1	

Methicillin-resistant *Staphylococcus aureus* (MLSBi -inducible resistance to clindamycin strains) + *Enterobacter cloacae*	*Staphylococcus aureus* + *Enterobacteriaceae*	1	
Staphylococcus epidermidis	*Staphylococcus spp*	6	
Staphylococcus epidermidis + *Pseudomonas fluorescens*	*Staphylococcus spp*	1	Partial identification
Staphylococcus lentus	*Staphylococcus spp*	2	
Ralstonia pickettii	-	0	The kit doesn't contain beacons for the identification of *Ralstonia pickettii* strains
Ralstonia pickettii + *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*	1	Partial identification
Klebsiella spp.	Enterobacteriaceae	1	
Enterococcus faecalis	*Enterococcus faecalis*	2	
Staphylococcus xylosus + *Acientobacter* spp.	*Staphylococcus* spp + *Acientobacter* spp.	1	
Enterobacter amnigenus 2	Enterobacteriaceae	1	
Enterobacter cloacae complex	Enterobacteriaceae	1	
Streptococcus group D	*Streptococcus* spp.	1	
Pseudomonas aeruginosa	*Pseudomonas aeruginosa*	1	
Escherichia coli	*Escherichia coli*	1	

The use of the 16S rRNA bbFISH® technology resulted in 26 positive (true-positive) and 30 negative (true-negative) tested samples. 5 samples were false negative, 4 of them in the context in which the kit does not contain beacons to identify the strains of *Ralstonia pickettii* and *Pseudomonas fluorescens*.

Regarding the performance of bacterial identification using molecular biology technique, in this case, 16S rRNA bbFISH (beacon-based fluorescent in situ hybridization) technology on samples of sonication fluid with using a bbFISH kit (hemoFISH® Masterpanel, miacom® diagnostics GmbH Düsseldorf, Germany), the sensitivity of this test is 83.87% (95% CI 66.27% - 94.55%) and the specificity is 100.00% (95% CI 88.43% - 100.00%) when analyzing the test/diagnostic procedure itself-, but when evaluating the same parameters strictly for bacteria that can be identified using this kit, the parameters are as follows: sensitivity of 100.00% (95% CI

86.77% - 100.00%), specificity is 100.00% (95% CI 90.00% - 100.00%), and accuracy is 100.00% (95% CI 94.13% - 100.00%).

The performance of the methods used to identify the etiological agents involved in the periprosthetic joint infections is different, data that already had been demonstrated and reported in the literature, and led to the need of using several methods of identification due to the fact that so far no method has a sensitivity and a specificity of 100%. Thus, in descending order of performance of bacterial identification methods used in this research study, the best parameters were identified for the sonication fluid cultures, followed by the molecular identification of bacteria using 16S rRNA bbFISH®, bacterial cultures from biopsy tissue samples of soft tissues as well as from the periprosthetic membrane of interface and cultures of the synovial fluid (sensitivity/ specificity: 90.32%/100.00%, 83.87%/100.00%, 80.65%/100.00%, and respectively 32.26%/100.00%).

4.6 Microbiological characteristics of isolated strains

The most important characteristic of a pathogen be it from the bacterial, fungal, or viral spectrum, is represented by the susceptibility, sensitivity, and resistance to the action of different classes of drugs.

The MICs (minimum inhibitory concentrations) of isolated bacterial strains were evaluated in accordance with the European Committee on Antimicrobial Susceptibility Testing breakpoints (EUCAST). Based on these minimal inhibitory concentrations, the susceptibility to antibiotics of the isolated strains was also established.

Multiple drug resistance (MDR)/ Extensively drug resistant (XDR)

28 bacterial strains from those isolated during the study period were multidrug-resistant bacterial strains (according to the definitions reported in the literature)

This grouping of bacterial strains according to resistance to different classes of antibiotics included 6 strains of Methicillin-resistant *S. aureus* (2 strains in 2016, 1 strain in 2018, and 3 strains in 2019), 6 strains of Methicillin-resistant *S. epidermidis* (2 strains in 2016, 1 strain each in 2017 and 2018, and 2 strains in 2019), and one strain of Methicillin-resistant *S. lentus*. 17 strains of Gram-negative bacilli were multiple drug resistance strains, of which 5 strains of ESBL (extended-spectrum beta-lactamases) type. One strain was Extensively drug resistant (XDR) ESBL (extended-spectrum beta-lactamases) the *Pseudomonas fluorescens* one. A Gram-negative MDR bacillus strain and an XDR strain were associated with a Methicillin-resistant *S. epidermidis* and Methicillin-resistant *S. aureus* strains subsequently being involved in the etiology of two cases of polymicrobial periprosthetic joint infection.

4.7 Comorbidities. Charlson Comorbidity Index

Comorbidities

In this study, a significant impact on the probability that patients would develop a periprosthetic joint infection was not associated with the underlying pathology (in terms of OR and RR values). In general, values of RR close to 1 suggest the same probability of getting the disease, so the factor has no influence. If RR has values greater than 1, there is a relationship between the risk factor and the disease (it is not mandatory to be the cause). OR values close to 1, denote that the exposure does not influence the appearance of the pathology, and a value well above 1, denotes a correlation tendency that is considered causal in most cases.

I also evaluated the possibility of a correlation between the number of comorbidities and the presence of a periprosthetic joint infection, there is no statistically significant correlation between these 2 parameters, r= 0.128, p= 0.326, n= 61. It was attempted to group the number of comorbidities into subgroups as follows: 1 comorbidity, 2 comorbidities, 3 comorbidities, and 4 or more comorbidities, and then re-evaluate the existence of a possible correlation. Even under these conditions in this research study, there is no statistically significant correlation between the number of comorbidities and the presence of a periprosthetic joint infection, r= 0.162, p= 0.213, n= 61.

The possibility of a statistically significant correlation between the average number of comorbidities or the average grouping of the number of comorbidities and the presence of a periprosthetic joint infection was also evaluated, but this association does not correlate with the same statistical parameters as above.

Although it is not one of the objectives of this research study, it is necessary to mention, as a reconfirmation, the fact that there is a statistically significant positive correlation between the age of patients and the number of comorbidities, r= 0.328, p= 0.010, n= 61.

In statistics, the logistic model is used to evaluate the probability of certain existing events, such as healthy-sick status of a person. In this research, the logistic model could be used to determine the probability of developing a periprosthetic joint infection. Based on the data in the table Variables in the Equation there is a probability for a smoking patient to develop a periprosthetic joint infection 0.001490 times higher (Exp(b)-*OR*), a statistically significant result, p= 0.04. The same probabilities are found in patients with ischemic heart disease (p= 0.020), body mass index greater than 30kg/m^2 (p= 0.038), liver disease (p= 0.027), seropositive rheumatoid arthritis (p= 0.025), and with an increased number of comorbidities (p= 0.048).

Charlson Comorbidity Index

Charlson Comorbidity Index is probably the most widely used index to predict ten-year mortality (estimated 10-year survival rate, expressed as a percentage) for a patient with several concomitant conditions. For the whole group of patients (n=61), the Charlson comorbidity index ranged from 0 to 7 points, with a mean of 3.97 and a standard deviation of ±1.449. The estimated 10-year survival rate ranged from 0 to 98% points, with a mean of 50.67% and a standard deviation of ±29.399%. The statistical analysis of these data does not show statistically significant differences between the 2 groups in terms of these 2 parameters (p= 0.218 for the Charlson

comorbidity index and p= 0.110 survival rate estimated at 10 years). In the group of patients diagnosed with periprosthetic joint infection (n=31) enrolled in the study, the Charlson comorbidity index ranged from 0 to 7 points, with a mean of 4 and a standard deviation of ±1.621. The estimated 10-year survival rate ranged from 0 to 98% points, with an average of 53.00% and a standard deviation of ±31.626%. In the group of patients diagnosed with aseptic loosening of the implant (n=30) enrolled in the study, the Charlson comorbidity index ranged from 1 to 7 points, with a mean of 4 and a standard deviation of ±1.230. The estimated 10-year survival rate ranged from 0 to 96% points, with a mean of 53.00% and a standard deviation of ±26.002%.

4.8 Therapeutic management

Therapeutic management of the patients diagnosed with periprosthetic joint infections.

All 31 cases of periprosthetic joint infections were analyzed from a therapeutic management point of view, a surgical procedure being associated with a specific antibiotic treatment in all cases, no patient being managed with long-term suppressive antibiotic therapy.

Therefore, the types of surgical management implemented, depending on the frequency, were: 1 3SE intervention - Three-stage exchange (3.22%), 4 DAIR interventions - Debridement and implant retention (12.90%), 12 OSE interventions - One-stage exchange (38.70%), and 14 TSE-interventions - Two-stage exchange (2-stage revision) (45.16%). In 2016, 6 TSE surgeries and one OSE surgery were performed. In 2017, 4 OSE surgeries were performed, and one OSE and 3SE surgery. 5 OSE surgeries, 3 TSE surgeries, and one DAIR surgery, were performed in 2018, and in 2019, 3 DAIR surgeries were performed, 2 OSE surgeries and 4 TSE surgeries.

Analyzing the type of surgical procedure implemented, depending on the type of periprosthetic joint infection (acute, chronic, or acute hematogenous), and the year of enrollment of the patients in the study, differences were observed in terms of the adopted treatment strategies, differences most likely occurred with increasing of the confidence level in the diagnostic and management strategies implemented through this research and with the publication, in the literature, of the long-term results obtained following the implementation of the same strategies in different reference centers at international level. If in the first 2 years of study, in the case of acute and acute hematogenous infections, the most frequently implemented surgical procedure was the OSE type, in the 2018-2019 study years the most frequently used surgical procedure was DAIR. In the case of chronic periprosthetic infections, if in the study period 2016-2017 the most common surgical procedure adopted was 2-stage exchange (TSE), in the last 2 years of study a definite change was observed towards the implementation of revision-type policies in single stage (OSE).

Table 9 Distribution of the number of type of surgeries by years of study and type of periprosthetic joint infection

Year of study: 2016	
Surgical intervention	Type of periprosthetic joint infection

	Acute	Acute hematogenous	Chronic
3SE - Three-stage exchange	-	-	-
TSE - Two-stage exchange	1	-	5
OSE - One-stage exchange	1	-	-
DAIR - Debridement and implant retention	-	-	-
Year of study: 2017			
Surgical intervention	Type of periprosthetic joint infection		
	Acute	Acute hematogenous	Chronic
3SE - Three-stage exchange	-	-	1
TSE - Two-stage exchange	-	-	1
OSE - One-stage exchange	1	1	2
DAIR - Debridement and implant retention	-	-	-
Year of study: 2018			
Surgical intervention	Type of periprosthetic joint infection		
	Acute	Acute hematogenous	Chronic
3SE - Three-stage exchange	-	-	-
TSE - Two-stage exchange	-	-	3
OSE - One-stage exchange	-	-	5
DAIR - Debridement and implant retention	-	1	-
Year of study: 2019			
Surgical intervention	Type of periprosthetic joint infection		
	Acute	Acute hematogenous	Chronic
3SE - Three-stage exchange	-	-	-
TSE - Two-stage exchange	-	-	3
OSE - One-stage exchange	-	-	2
DAIR - Debridement and implant retention	2	2	-
Total			
Surgical intervention	Type of periprosthetic joint infection		
	Acute	Acute hematogenous	Chronic
3SE - Three-stage exchange	-	-	1
TSE - Two-stage exchange	1	-	12
OSE - One-stage exchange	2	1	9
DAIR - Debridement and implant retention	2	3	-

The implemented therapeutic management failed in two cases.

Based on these two cases of failure of a periprosthetic joint infection surgical intervention, I can state that, in the case of this group of studied patients, the recurrence rate of a periprosthetic joint infection after a surgical intervention is 6.45%.

Intravenous antibiotic treatment included vancomycin in eighteen cases, ampicillin/sulbactam in two cases, and each of the following in one case: meropenem + linezolid, linezolid + levofloxacin, levofloxacin, vancomycin + meropenem, meropenem, piperacillin/tazobactam, and vancomycin + cefuroxime. The most commonly prescribed oral antibiotic was cotrimoxazole in 10 episodes, followed by cotrimoxazole + rifampicin in 6 episodes, levofloxacin in 5 episodes, levofloxacin + rifampicin in 4 episodes, and each in a single episode: ciprofloxacin, cotrimoxazole + cefuroxime, amoxicillin/clavulanic acid, and amoxicillin/clavulanic acid + cotrimoxazole. The total duration of the antibiotic treatment was 3 months, except in one case.

4.9 Follow-up

Patients were followed and evaluated postoperatively until they developed treatment failure, died, or were lost during the follow-up period. During the study period from the available documents no patient died, and no patient was lost during study.

Kaplan-Meier analysis of the entire study group

Using the cumulative survival table, the probability of cumulative mortality at 12 months is 1.60%, at 25 months 3.40% and at 39 months 3.40% or the probability of cumulative survival at 12 months is 98.40% at 25 months of 95.30% and at 39 months of 95.30%.

Kaplan-Meier analysis by study groups

This analysis was performed on the two study groups, patients diagnosed with aseptic loosening and patients diagnosed with periprosthetic joint infection using the following steps - KM Luni BY infectie /STATUS=Recidivă(0) /PRINT TABLE MEAN /PLOT SURVIVAL /TEST LOGRANK BRESLOW TARONE /COMPARE OVERALL POOLED.

Using the cumulative survival table again, the probability of cumulative mortality in patients diagnosed with aseptic loosening of the endoprosthetic implant at 12 months is 0.00%, at 25 months is 0.00%, and at 39 months is 0.00% or the probability of cumulative survival at 12 months is 100.00%, at 25 months is 100.00%, and at 39 months is 100.00%, and in the case of patients diagnosed with periprosthetic joint infection the probability of cumulative mortality at 12 months is 3.20%, at 25 months is 8.30% and at 39 months is 8.30% or the cumulative survival probability at 12 months is 96.80%, at 25 months is 88.70%, and at 39 months is 88.70%.

Kaplan-Meier analysis by study groups and surgical interventions

This analysis was performed on the two study groups, patients diagnosed with aseptic loosening and patients diagnosed with periprosthetic joint infection using the following steps - KM Luni BY infectie /STRATA=Procedeuch /STATUS=Recidivă(0) /PRINT TABLE MEAN /PLOT SURVIVAL /TEST LOGRANK BRESLOW TARONE /COMPARE OVERALL POOLED.

Analyzing the cumulative survival table, the only events that were present when using a TSE-Two-stage exchange surgical procedure.

Using the cumulative survival table, the probability of cumulative mortality, in the case of patients in whom a surgical procedure other than the Two-stage exchange was used, is 0.00% at 12 months, 0.00% at 25 months, and 0.00% at 39 months or the cumulative survival probability at 12 months is 100.00%, at 25 months is 100.00%, and at 39 months is 100.00%, and in the case of patients in whom the TSE-Two-stage exchange surgical procedure was used, (a procedure used strictly in patients with periprosthetic joint infection) the probability of cumulative mortality at 12 months is 6.9%, at 25 months it is 15.20%, and at 39 months is 15.20% or the probability of cumulative survival at 12 months is 92.90%, at 25 months is 77.40%, and at 39 months is 77.40%. It should be recalled that this type of therapeutic management implemented, failed in two cases. In the first case, the failure was caused by a lack of compliance with the antibiotic regimen (the patient giving up ciprofloxacin therapy at home after 30 days) and in the context of being an immunocompromised patient in the context of immunosuppression for a kidney transplant. The second case, a periprosthetic joint infection caused by a bacterial strain of *Enterococcus faecalis* managed by a two-stage exchange procedure, reinfection caused by the same strain of *Enterococcus faecalis*.

Therefore, I can summarize the fact that using the Kaplan-Meier estimation function, the estimated survival rate (translated in the case of this research by the absence of recurrence of periprosthetic joint infection) compared to the type of surgical procedure used and at 39 months is 100.00% in the case of Debridement and implant retention type, One-stage exchange, and Three-stage exchange type of surgery, and in the case of the Two-stage exchange procedure also at 39 months this rate is 77.40%.

4.10 Economic implications. Hospitalization period.

Treatment cost

Using again a one-way ANOVA statistical analysis procedure and then the multiple comparisons table containing the results of a Tukey post hoc analysis test I can conclude that there is a statistically significant correlation between the cost of management of a patient and the presence of a periprosthetic joint infection (p=0.000), so the management costs of a patient were associated with the diagnosis of periprosthetic joint infection.

Hospitalization period

Another parameter with major implications in the economic burden of periprosthetic joint infections as well as in all pathologies is represented by the hospitalization period. A factor that can decisively influence the evolution of any pathology.

The average duration of hospitalization of a patient with a periprosthetic joint infection, depending on the surgical chosen procedure, was 9.5 days, 12.25 days, and 26.71 days for DAIR, OSE, and TSE, respectively.

Longer hospitalization periods were at patients diagnosed with periprosthetic joint infections (over 25 days) were associated with the following isolated bacterial strains: Methicillin-resistant *Staphylococcus aureus* (MLSBi -inducible resistance to clindamycin strains); Methicillin-resistant *Staphylococcus aureus* (MLSBi -inducible resistance to clindamycin strains) + *Enterobacter cloacae* complex; *Staphylococcus epidermidis; Staphylococcus epidermidis* + *Pseudomonas fluorescens*; *Staphylococcus lentus*; *Ralstonia pickettii*, and *Enterococcus faecalis*.

Using again a one-way ANOVA statistical analysis procedure and the multiple comparisons table containing the results of a Tukey post hoc analysis test I can conclude that there is a statistically significant correlation/difference between a patient's hospitalization period and the presence of a periprosthetic joint infection ($p= 0.048$), so long hospitalization periods of a patient were associated with the diagnosis of periprosthetic joint infection.

Using a bivariate correlation procedure, with the calculation of Pearson, Kendall's tau-b or Sperman correlation coefficients, and the use of a significance test, no statistically significant correlation was found between the length of hospital stay and the type of surgical procedure used.

6. DISCUSSIONS

The age of patients undergoing primary joint replacement surgery has decreased significantly in recent decades. This was due, on the one hand, to the good survival rate of primary implants, and, on the other hand, to the growing expectations of patients (269).

The diagnosis and management of prosthetic joint infections remain an issue. The existence of the "window" of 3 weeks is a key time point in which we either won the fight for the "surface" or we lost it. Protocols adapted to the treatment of biofilm-associated infections and new diagnostic methods have improved the rate of eradication of infections, without having a 100% certainty that we have eradicated the infection. Well-equipped treatment centers for diagnosis and multidisciplinary teams of surgeons-infectious disease specialist - clinical microbiologists are needed. Periprosthetic joint infections are the most feared complication associated with arthroplasty and require an early, rapid, and accurate diagnosis, able to lead to the implementation of an adapted therapeutic management strategy.

The diagnosis of periprosthetic infection is based on a number of well-defined criteria (91) (270) (271). So far, there is no clearly defined gold standard to establish the diagnosis of biofilm-associated orthopedic implant infections, although the First and Second International Consensus has been able to standardize to a greater extent the diagnosis and the management of these cases ((272). It is mandatory, for the management of cases of periprosthetic joint infections, to consider a multidisciplinary approach (orthopedic surgeon - infectious disease specialist - clinical microbiologist) (91).

Although the implementation of standardized strategies and local or national/international diagnostic and management protocols, such as the use of laminar flow operating rooms, or the appropriate administration of antibiotics perioperatively, has contributed to a decrease in the incidence of periprosthetic joint infection, it continues to show up.

The incidence of periprosthetic joint infection after primary total hip arthroplasty is 1-2% (273; 274; 275), while the rate of periprosthetic joint infection after primary total knee arthroplasty is 1-4% (275; 276; 277; 278). Periprosthetic joint infection represents 14.8% of the revisions performed for hip arthroplasty and is the most common cause of revision after knee arthroplasty (25.2%) (279; 280).

A monocentric, observational, cohort study was conducted in the Academic Emergency Hospital Sibiu, Romania, study in which there was enrolled a total of 61 patients during the study period (September 2016 - January 2019), representing a total number of 61 retrieved implants. Based on the diagnostic criteria, the patients were separated into two groups. The diagnosis of aseptic loosening of an endoprosthetic implant was established in 30 cases (49.18%) and the diagnosis of orthopedic implant-associated infections (periprosthetic joint infection) was established in 31 cases (50.81%). In the subgroup of patients diagnosed with aseptic loosening, the mean age of the enrolled patients was 68.50 years and in the subgroup of patients diagnosed with a periprosthetic joint infection, the mean age of the patients was 68 years. Using the classification proposed by Zimmerli et al. (236), the 31 patients diagnosed with periprosthetic joint

infection were classified as follows: 9 patients diagnosed with early periprosthetic joint infection, 6 patients with delayed periprosthetic joint infection and 16 patients diagnosed with late periprosthetic joint infection.

The study of the synovial fluid is a key element in establishing the diagnosis of periprosthetic joint infection. Synovial fluid for this study was analyzed for cellularity, C-reactive protein levels, and leukocyte esterase.

My study also had some limitations. First of all, the type of the conducted study, a monocentric, observational, cohort study. Second, the small population of enrolled patients in the study, respectively the number of cases with periprosthetic joint infections enrolled in the study associated with a relatively short period of enrollment and follow-up. Thirdly, the center where this study was conducted is not a dedicated center for the treatment of periprosthetic joint infections, but with the introduction of the new protocol and the dedicated team to manage these cases (orthopedic surgeon - infectious disease specialist - microbiologist), the results are encouraging, the prevalence of periprosthetic joint infections in the population may be even higher. Fourth, each method analyzed in this study has a limitation, such as the test with leukocyte esterase detection strips maybe limited by the ability to read its color due to the presence of blood or tissues, or the molecular detection 16S rRNA bbFISH (beacon-based fluorescent in situ hybridization) technology and in this case the bbFISH kit (hemoFISH® Masterpanel, miacom® diagnostics GmbH Düsseldorf, Germany used, can strictly detect the bacteria for which this kit was developed. Fifth, the estimated cost of managing these cases did not include the costs of other hospitalizations (eg, hospitalizations in the Infectious Diseases Departments), nor did it include the costs of outpatient assessments, including rehabilitation, home care, and outpatient pharmaceutical treatments. Regarding the estimated costs, the economic burden of the periprosthetic joint infection calculated in the present study is definitely underestimated. Many social and economic factors can influence population changes. Larger studies are needed to confirm these results. However, my results are very promising.

7. CONCLUSIONS.

It was a long journey to understand the mysterious world of biofilms, a journey with many discoveries in this field. There is new, extraordinary information that involves the knowledge of cell-to-cell communication, but we are still at the beginning of our understanding. These findings will definitely advances in the treatment of biofilm-associated infections.

The diagnosis and management of orthopedic implants associated infections, biofilm-related infections remain a problem. Periprosthetic joint infection remains the most common and dreaded complication associated with an arthroplasty. Despite scientific progress in recent years, the incidence of periprosthetic joint infections is increasing, both due to an increased number of primary endoprosthesis interventions and the emergence of microorganisms that resistant to different classes of antibiotics or even pan-resistant. Diagnostic and treatment centers dedicated to the management of periprosthetic joint infections with multidisciplinary teams (orthopedic surgeon, infectious disease specialist, and clinical microbiologist) are mandatory to offer the chance of correct orthopedic management of biofilm-associated infections with endoprosthetic implants.

Bacterial cultures of the sonication fluid remain the gold standard in diagnosing periprosthetic joint infections. A negative culture of the preoperative harvested synovial fluid, or the soft tissues surrounding the endoprosthetic implant or of the implant-bone interface membrane obtained intraoperatively, does not exclude the presence of bacteria on the implant surface. Molecular detection technology of the bacteria like 16S rRNA bbFISH (beacon-based fluorescent in situ hybridization) is a successful new molecular assay that complements traditional approaches and accelerates the diagnosis of periprosthetic joint infections. These 16S rRNA bbFISH assays should be optimized for the detection of bacterial strains relevant to the field of orthopedic implant infections like *Cutibacterium* (previously known as *Propionibacterium*) acnes, and why not *Ralstonia pickettii* or *Pseudomonas* spp.

Determining the level of the C-reactive protein in synovial fluid showed the best performance in terms of sensitivity, followed by leukocyte count, polymorphonuclear percentage, and leukocyte esterase. In terms of specificity, the highest value was found when determining the number of leukocytes, followed by leukocyte esterase, the percentage of polymorphonuclear, and finally the level of C-reactive protein in synovial fluid. The leukocyte esterase strip test proved to be at least satisfactory, as it is a fast test and less expensive, and is a good option compared to the costs of detecting C-reactive protein from the synovial fluid. Published data on the level of C-reactive protein in synovial fluid show that each center should set its own threshold values because, as other authors have reported, its determination appears to be influenced by the method used for the detection. Both leukocyte esterase and C-reactive protein from the synovial fluid have a high diagnostic value. Both the number of leukocytes from the synovial fluid and the percentage of polymorphonuclear cells in the synovial fluid maintain their role in the diagnosis of periprosthetic joint infection. The detection of leukocyte esterase, the number of leukocytes from the synovial fluid, and the percentage of polymorphonuclear in the synovial fluid is reliable and valid, synovial fluid C-reactive protein levels still need to be evaluated.

Probably the biggest contribution to the implementation of this diagnostic strategy was the possibility of identifying and managing cases of periprosthetic joint infections caused by very rare pathogens identified, among them, the 4 cases of periprosthetic joint infections caused by *Ralstonia pickettii* a Gram-negative bacillus with the ability to form biofilms, which was extremely rarely involved as an etiological agent in such situations. At the same time, based on my observations, together with the infectious disease specialist involved in the project, I was able to establish the drug (antibiotic) management strategy of these cases, as there are no international guidelines or recommendations so far.

The implementation of this strategy for diagnosis and treatment of patients with periprosthetic joint infections, from my point of view, was a real success for patients, the use of the techniques implemented below will depend only on the desire of the professionals involved in the management of these cases. The use of the protocol created except the routine use of the molecular detection technique of bacteria from my point of view is mandatory when it is desired to treat patients with periprosthetic joint infections. This paper will be the starting point for my future scientific research.

In conclusion:

1. Periprosthetic joint infection remains the most common and dreaded complication associated with arthroplasty.
2. From the total number of 61 implants retrieved, 58 were endoprosthesis type implants and PMMA/polymethylmethacrylate spacers 3, the diagnosis of aseptic loosening of an endoprosthetic implant was established in 30 cases (49.18%) and the diagnosis of periprosthetic joint infection was established in 31 cases (50.81%).
3. The mean age in the group of patients diagnosed with aseptic loosening was 68.50 years and in the group of patients diagnosed with a periprosthetic joint infection, the mean age of patients was 68 years.
4. 22 patients were female patients and 17 patients were from rural areas in the first group, respectively 10 patients were female patients and 15 patients were from rural areas in the second group.
5. There were no statistically significant differences between the 2 study groups related to age or residence are, p=0.574, respectively p=0.517. From the gender point of view, there were statistically significant differences between the 2 groups, p=0.001.
6. Between the time of the primary intervention and the enrollment in the study between the two study groups, there were significant differences, p=0.010 and, respectively, p=0.018.
7. The underlying joint pathology, in the group of patients diagnosed with aseptic loosening of an endoprosthetic implant, was osteoarthritis (n=22), followed by rheumatoid arthritis (n=6) and trauma - femoral neck fracture (n=2), and in the group of patients diagnosed with

periprosthetic joint infection, the most common pathology was osteoarthritis (n=28), followed by rheumatoid arthritis (n=2) and trauma - femoral neck fracture (n=1).

8. The average duration in years from the time of the primary endoprosthetic intervention until the onset of the periprosthetic joint infection symptomatology was 3.23 years, with a minimum of 2 weeks and a maximum of 15 years.
9. Among the comorbidities present in the study population, the risk of developing a periprosthetic joint infection in patients with ischemic heart disease - a risk of 0.077 times higher 95% CI [0.008 - 0.0765] p=0.029, and in patients with seropositive rheumatoid arthritis – a risk of 0.040 times higher 95% CI [0.002 - 0.716] p=0.029.
10. The level of the C-reactive protein from the synovial fluid showed the best performance in terms of sensitivity, followed by the number of leukocytes, polymorphonuclear cells, and leukocyte esterase.
11. In patients diagnosed with aseptic loosening, the number of leukocytes in the synovial fluid was 645.27 G/l (± 502.53), versus 8962.58 G/l (± 9488.41), in those with periprosthetic joint infections.
12. The average percentage of polymorphonuclear neutrophils (PMN) in the synovial fluid was 52% (± 6.27) in patients with aseptic loosening, versus 82.29% (±13.00) in those with periprosthetic joint infections, statistically significant - p=0.000.
13. In the case of acute periprosthetic joint infection, the mean C-reactive protein in synovial fluid was 81.40 mg/L, the mean number of leukocytes in synovial fluid was 19700.00 G/l (±10207.97), and the average percentage of polymorphonuclear neutrophils in the synovial fluid was 90% (±3.53).
14. In patients diagnosed with an acute hematogenous periprosthetic joint infection, the mean C-reactive protein in synovial fluid was 36 mg/L the mean number of leukocytes in synovial fluid was 17000.00 G/l (± 10923.97), and the mean percentage of polymorphonuclear in the synovial fluid was 91.25 (±2.50).
15. In patients diagnosed with a chronic periprosthetic joint infection, the mean C-reactive protein in synovial fluid was 8.96 mg/L, the mean number of leukocytes in synovial fluid was 5060.90 G/l (± 6002.32), and the mean percentage of polymorphonuclear was 78.92% (±14.02).
16. Regarding the above-evaluated parameters, there are statistically significant differences between the levels of these parameters concerning the types of infections, p=0.000.
17. A statistically significant correlation between the C-reactive protein serum level and the presence of a periprosthetic infection, r= 0.378, p= 0.003, n= 61.
18. There is a statistically significant correlation between increased erythrocyte sedimentation rate and the presence of a periprosthetic joint infection, r= 0.304, p= 0.017, n= 61.

19. Between the two groups of patients, there were statistically significant differences in fibrinogen levels, p= 0.017, and a statistically significant correlation between fibrinogen levels and the presence of a periprosthetic joint infection, *r*= 0.305, p= 0.017, n= 61.

20. From a histopathological point of view, there is a statistically significant correlation between type II periprosthetic membrane and the presence of a periprosthetic joint infection (p=0.005), as well as the fact that type IV periprosthetic membrane is more frequently associated with cases of mechanical implant orthopedic endoprosthetic loosening (p=0.016).

21. An etiological diagnosis was possible in 29 of the 31 cases of periprosthetic joint infections (93.54%).

22. The most common Gram-positive cocci isolated were: *Staphylococcus aureus* (n=7), *Enterococcus* spp. (n=2), *Streptococcus* grup D (n=1), and *Staphylococcus epidermidis* (n=7).

23. Gram-negative bacilli isolated in periprosthetic joint infections were represented by *Escherichia coli*, *Enterobacter* (spp., *E. cloacae* complex, *E. amnigenus*), *Klebsiella* spp., *Pseudomonas fluorescens*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Ralstonia pickettii*.

24. Regarding the performance of the sonication fluid culture, the sensitivity of this test is 90.32% and the specificity is 100.00%. Sonication allowed the identification of 4 strains of *Raltsonia picketti*, not identified by classical methods.

25. 18 strains of aerobic Gram-positive cocci and 6 strains of aerobic Gram-negative bacilli were also isolated from biopsy tissue cultures, the most commonly identified were *Staphylococcus aureus* (n=7), and *Staphylococcus epidermidis* (n=6).

26. The optimal number of samples taken intraoperatively is 5.

27. Blood cultures and bacteriological examination of the sonication fluid identified the same pathogen in 3 patients, namely: *Klebsiella* spp., Methicillin-resistant *Staphylococcus aureus*, and *Staphylococcus epidermidis*.

28. 30 bacterial strains from those isolated during the study were multidrug resistant strains: 6 strains of MRSA, 7 strains of coagulase-negative staphylococci, 17 Gram-negative bacilli, of which 3 strains of *Ralstonia picketti*.

29. The 16S rRNA bbFISH molecular detection techniques accelerate the diagnosis of periprosthetic joint infection – requires *Cutibacterium acnes*, *Ralstonia pickettii*, or *Pseudomonas* spp.

30. The best parameters were identified for the sonication fluid cultures, followed by molecular biology detection techniques for identifying bacteria by 16S bbFISH® rRNA, bacterial cultures from biopsy tissues, and cultures of the synovial fluid.

31. The recurrence rate of periprosthetic joint infection after management was 6.45%.

32. The average length of hospitalization of the enrolled cases was 15.98 days with a minimum of 7 days and a maximum length of hospitalization of 66 days; for periprosthetic joint infections, it was 18.87 days, with a standard deviation of ±14.61 days.

33. Longer hospitalization periods over 25 days were associated with *Staphylococcus aureus* or coagulase-negative staphylococci infections, microbial associations, and infections with *Pseudomonas fluorescens*, *Ralstonia pickettii*, and *Enterococcus faecalis*.

34. The cumulative survival probability at 12 months is 92.90%, at 25 months it is 77.40%, and at 39 months it is 77.40%.

35. Based on the observations in this study, the identification of etiological agents such as *Ralstonia pickettii*, I concluded that the introduction of ciprofloxacin into spacers in combination with aminoglycosides or vancomycin is the best option to extend the antibacterial efficacy against opportunistic germs.

36. Diagnostic and treatment centers dedicated to the management of periprosthetic joint infections with multidisciplinary teams (orthopedic surgeon, infectious disease specialist, and clinical microbiologist) are mandatory to provide the chance for a correct orthopedic management of biofilm-associated endoprosthetic implants infections.

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