UNIVERSITATEA LUCIAN BLAGA DIN SIBIU

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Ph. D. Thesis

# Postoperative complications of hip and kee arthroplasties

# Summary

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# CUPRINS

# INTRODUCTION

## HIP

Hip arthroplasty has undergone numerous changes, the progression of which has been guided by both technical and scientific progress and the level of experience in orthopaedic surgery. The procedure results in a new joint which, although not up to the level of the physiologic one, is still relatively functional. Today, total hip arthroplasty is considered to be the most widely used reconstructive procedure for the adult hip, representing a quality treatment for a variety of conditions, with coxarthrosis (including post-traumatic) remaining the most common indication. Hip arthroplasty is all the safer because the indications for the procedure have been more rationally realized, using general and local objectives. To perform such an intervention, it is necessary to balance the risks and benefits of the intervention so that the benefits clearly outweigh the risks; for patients over 60 years of age who are not highly active, the effects of hip joint replacement have become remarkable and long-lasting. For the vast majority, arthroplasty remains the only interventional option, with the revision rate becoming almost nil, hence the indications for endoprosthesis are major. As the activity level is higher in patients aged between 40 and 60 years, and the implant cannot survive as long as the longevity of the hip prosthesis, the risk of prosthetic revision remains high [1].

## KNEE

The pathologies and traumas of the human skeletal skeleton are responsible for a decrease in the population's quality of life, and for some patients, the only solution to eliminate pain and restore the functions of the affected organ is prosthetic surgery. Theoretical and experimental studies are being carried out worldwide in the fields of prosthetics for the design and realization of implants. Depending on the degenerative pathology of the joint, it is partially or totally replaced with an endoprosthesis [2]. Partial arthroplasty involves replacing a single condyle and its meniscus with a unicompartmental knee prosthesis. Total arthroplasty involves replacing both joint condyles and menisci with the metal and plastic components of a total knee replacement.

## Motivation for choosing the research theme

Considered the flagship surgeries of modern medicine, hip and knee arthroplasty are now considered safe and effective procedures that offer patients full reintegration into daily activities. According to analysis by OECD Publishing, the number of these surgical procedures has almost doubled between 2000 and 2015 worldwide, with data collected from both public and private hospitals.Din dorința de a oferi pacienților un serviciu medical performant, atenția mai multor centre medicale s-a îndreptat spre prevenirea complicațiilor ce sunt asociate acestor proceduri ortopedice.

One of the dreaded complications that can occur after stent graft surgery is periprosthetic infection, which has the potential to be a life-threatening complication for the patient and also poses a challenge for the doctor, being difficult both to diagnose and treat. However, the earlier the diagnosis, the better the chances of successful treatment.

Thus one of the objectives of this work is to monitor post-operatively the variation of C-reactive protein, fibrinogen and hema sedimentation rate in order to obtain additional information that may benefit the patient in early diagnosis of infectious complications and their treatment including the influence of hospitalization costs.

Another aim is to analyze preoperative asymptomatic infections and to demonstrate a link between them and the possibility of reducing periprosthetic infections.

The risk of bleeding and hematoma is also present in hip reconstruction surgery. Vascular complications are among the most common, both in patients with various comorbidities requiring anticoagulants and in patients with no significant pathologic history.

Deep vein thrombosis (DVT) and pulmonary embolism (PE) occur in 0.6-3.0% of cases following total hip arthroplasty and total knee arthroplasty.

We analyze the dose-dependent efficacy of tranexamic acid in patients who underwent hip and knee arthroplasty and whether the risk of DVT is higher with dose.

# CHAPTER 1

# 1. General considerations about total knee and hip arthroplasty

## 1.1. General and epidemiologic data of hip and knee arthroplasty

Total hip and knee arthroplasty has been widely performed since the 70s. In 2009, over one million total hip and knee arthroplasties were performed in the United States [3]. Because these procedures are elective and costly (approximately $3.2 billion was paid in 2000 for hip and knee joint replacement), and because the prevalence of arthritis is expected to increase substantially as the population ages, these procedures are likely to be subject to increased scrutiny and observation [4].

Between 1996-1998 and 2004-2006, in the United States, the number of people reporting a musculoskeletal disorder increased by about 14 million, from the 76 million reported in 1996. Among the main subgroups of musculoskeletal diseases, arthritis and joint pain have the highest occurrence, reflecting the ageing of the population [5].

In 2007, Kurtz et al. conducted statistical studies, based on a national historical data from 1990 to 2003, on the number of total hip replacements and hip revisions to be performed between 2005 and 2030. 202,500 total hip replacements and 36,000 hip revisions were performed in 2003. According to the study, the demand for total hip arthroplasty is expected to increase by 174%, from 208,600 total hip replacements in 2005 to 572,000 in 2030, and from 40,800 revisions in 2005 to 96,700 in 2030 [6].

Over time, there has been an increased prevalence of osteoarthritis of the hip, knee and hand in females compared to males. However, the reasons why females are more affected are still unclear, but a prevalence of various forms of congenital hip dysplasia in females and an increased risk due to changes in endogenous estrogen production and the onset of menopause are considered to be prevalent [7].

Currently, there is no way to prevent primary coxarthrosis completely. Treatment includes symptom relief and consists of a combination of patient education, physiotherapy, weight control, the use of medication and, finally, total hip joint replacement [8].

In terms of secondary osteoarthrosis, the most common conditions that can lead to this pathology are: osteonecrosis of the femoral head, inflammatory arthritis, hemoglobinopathies, various metabolic disorders, osteoporosis and congenital malformations of the hip [9].

The main cause in the onset of gonarthrosis, as in other forms of arthrosis, is the disruption of the functional balance between the mechanical pressure exerted on the articular cartilage and the biological capacities of the cartilage, leading to degeneration and destruction over time [10]. Four components of the synovial joint participate in this pathology. These are: the meniscus (the majority of synovial joints), articular cartilage, subchondral bone and the synovial membrane. In a healthy joint, these components support the joint. The menisci provide several functions, including weight bearing

and shock absorption in the knee joint. Articular cartilage provides a surface for synovial joint movement. It is divided into deep, middle and superficial zones, characterized by differences in matrix composition and cell orientation. The subchondral bone supports the joint and is composed of mineralized collagen type I. The synovial membrane (synovium) produces synovial fluid; this fluid, which is composed of lubricin and hyaluronic acid, lubricates the joint and nourishes the articular cartilage [11].

Degradation of articular cartilage in the knee joint through progressive wear and tear is a common cause of joint deformity with significant repercussions on patients' quality of life. Although its management provides for a conservative treatment modality, depending on the degree of damage, remarkable results have been recorded following the introduction of total knee arthroplasty as a therapeutic option.

Total knee arthroplasty is considered a safe and effective operation, with a reported incidence in Romania of 8.8 operations per 100,000 people in 2011, data collected by Steven M. Kurtz and his collaborators [6]. Severe complications associated with this surgery are reported by the American Academy of Orthopaedic Surgeons to occur at a rate of 2% of cases. The most common complications are the risk of bleeding, infections described in the literature (between 1% and 10%), pulmonary thromboembolism and venous thrombosis.

### 1.2. Hip arthroplasty after proximal femur fractures

Fracture of the proximal femur is one of the most common traumatic pathologies seen in elderly patients and is associated with increased mortality and morbidity. According to epidemiologic data, in 1990 the number of hip fractures globally was estimated at 1.66 million, and it is predicted that by 2050 the annual number of new cases will reach 6.26 million. The incidence by sex is 2-3 times higher in females than males. It can also occur in younger people as a result of a strong, high-intensity trauma, but in over 90% of cases it occurs in people over 50 and is caused by minor trauma, a phenomenon explained by the deterioration of bone tissue with age, namely a decrease in its hardness and elasticity.

Fractures of the proximal femur are divided into three categories according to their anatomical position: femoral neck fractures, intertrochanteric fractures and trochanteric fractures, each of which requires specific treatment and has different possible complications.

Femoral neck fractures are located between the femoral head and the intertrochanteric region and are further divided into two categories with different surgical treatment options: femoral neck fractures in young patients and femoral neck fractures in elderly patients, for the latter the treatment of choice is hip arthroplasty.

## 2. General considerations about complications of total knee and hip arthroplasty

The most common post-operative complications are:

Hip prosthesis dislocation is one of the main reasons for revision surgery. It is defined as the

complete loss of contact between the two components of the artificial joint. 70% of dislocations occur within the first month after surgery. The rate of dislocation is higher in arthroplasties performed after fractures of the proximal femur than after other bone pathologies. In addition, they occur more frequently in older patients, in females and in those who have had previous surgery [20].

Intraoperative periprosthetic fractures are challenging complications that can affect implant stability and survival. The widespread use of cementless acetabular cups may lead to a higher number of fractures than is clinically detectable. Several patient characteristics are associated with an increased risk of periprosthetic fractures. Female sex and increased age are independent and unmodifiable risk factors. Osteoporosis and poor bone quality also lead to an increased fracture risk [21].

Infections associated with hip arthroplasty fall into two main categories: early infections - occurring within the first three months after surgery and late infections - occurring more than three months after surgery. The risk of developing an infection remains despite the healing of the lesions, but it is not as high, with the possibility of contamination of the prosthesis even several years after the operation through hematogenous spread of bacterial infections from different organs. Infections can be superficial, when only the soft parts are involved, which can be treated with antibiotics alone, or deep, when the prosthesis chamber is involved, which is serious and requires further surgery to remove the infected components. Patients suffering from obesity, diabetes, anemia or inflammatory diseases are at higher risk [22].

Deep vein thrombosis and pulmonary embolism are severe complications that can occur after total hip arthroplasty. The surgery itself and prolonged bed immobilization contribute to thrombus formation along with a number of predisposing factors including age over 60, venous insufficiency, obesity, hyperlipidemia, oral contraceptive treatment and genetic factors. Routine thromboprophylaxis with aspirin, warfarin and low molecular weight heparins is recommended for patients undergoing hip replacement surgery [23].

Aseptic stent graft loosening is one of the most serious late complications. It is the progressive migration of the implant over time in the absence of infection. Aseptic loosening is frequently associated with osteolysis and requires revision surgery involving replacement of the weakened elements [24].

## 2.1. Deep vein thrombosis

In spite of prophylaxis, deep vein thrombosis is a serious complication associated with this procedure, and thrombus migration into the systemic circulation and pulmonary thromboembolism remain common complications. Data published in 2004 by the American College of Cardiologists reflect an incidence of pulmonary thromboembolism ranging from 0.9% and 28% respectively for hip arthroplasty and from 1.5% and 10% respectively for knee arthroplasty. Surgical intervention and immobilization for a prolonged period of time are factors favoring thrombus development in deep veins. Furthermore, a 1.9% incidence of acute myocardial infarction after total hip arthroplasty is also described in the literature.

The risk of pulmonary thromboembolism remains associated with orthopaedic interventions despite prophylaxis. Total knee arthroplasty is considered a major factor in the pathophysiologic mechanism of thrombus development. The rate of occurrence of deep vein thrombosis reported in the literature 90 days after surgery is less than 4%.

Diagnosis and management of thromboembolic complications secondary to total hip and knee arthroplasty remain a problem. No single therapeutic agent or combination of therapies decreases the rate of occurrence of deep vein thrombosis to 0%.

Various studies have been carried out over the years on the use of biological parameters for the early determination of complications in total hip or total knee arthroplasty.

## 2.2. Periprotic infections

Infection is one of the early preoperative complications when it is limited to soft tissues or may have a slower evolution when it includes endoprosthetic components. The rate of deep-seated infection described in the literature is between 1% and 10%, which is influenced by a number of prophylactic measures such as preoperative antibiotic therapy, irrigation of bone surfaces with saline after osteotomy and fixation of prostheses.

The number of total arthroplasties is increasing and with it the number of septic complications. At the same time, the profile of bacterial resistance to antibiotics is changing, which is why prevention and early treatment of infections is important. In order to establish the therapeutic attitude, it is important to diagnose as early as possible, so that in the first 4 weeks a conservative approach can be followed because the microorganisms are not yet organized in biofilms, while a late diagnosis, after more than 4 weeks, may require the need to remove the prosthesis due to the production of microbial biofilm resistant to antibiotic therapy and host defense mechanisms.

Periprosthetic infections are a life-threatening pathology (responsible for 15% of hip arthroplasty failures). At the same time, they are a rare pathology, occurring in only 1-2% of hip arthroplasty cases. This type of pathology can be treated conservatively or aggressively, depending on the degree of tissue damage and the patient's condition. Targeted antibiotic therapy with irrigation and debridement of the affected tissues may be tried, but the chances of success are relatively low (this type of treatment works if the infection has only affected small areas of tissue). In severe cases, a one-stage or two-stage revision using antibiotic-loaded acrylic cement or the Girdlestone operation, which is quite mutilating, the patient losing the function of the operated limb [59].

Currently, the gold standard for prosthesis infection is to perform a two-step revision, the first step being to debride and remove the dead or pathogen-affected tissues and insert an antibiotic-loaded cement into the remaining cavity, which will achieve a very high discharge of active substance (which cannot be done i.v.). In addition, this antibiotic spacer does not allow such significant muscle retraction and provides some preservation of function of the affected limb. The antibiotic spacer can be made in the operating room itself from antibiotic-loaded cement, or it can be supplied prefabricated from a manufacturer, similar in shape to the prosthesis previously used [60]. After a period of time, once there is the assurance of an infection-free zone, one continues with the second time, when the actual revision is performed. In the US literature, the success rate of two-stage revision is 85-95%, but

we have to take into account one very important aspect. Both Leung et al. and Touloson et al. reported a 24% and 25.8% death rate, respectively, in the evaluation of patients who underwent two-stage revision two years after surgery, and Berend et al. reported a 45% death rate at a mean of 4.7 years after surgery. Thus, although eradication of infection and restoration of the segment are basic desires, the patient, and his or her ability to withstand such a resource-consuming operation, must also be considered [61], [62], [63].

The idea of introducing antibiotics into the cement used for prostheses and then into the spacer used in the revision of periprosthetic infections originated in 1970 (Bucholtz and Engelbrecht). Since then, a lot of studies have been done on the subject and it has been observed that 90% of infections are eradicated, so it has become the gold standard. Unfortunately, two-stage revision is associated with an increase in morbidity, so a proper weighing of all factors and an understanding of the patient and their associated pathology are needed [64].

When discussing a periprosthetic infection, rapid diagnosis is the key to instituting correct treatment. There are some signs of certainty: one of the clearest is the presence of a fistulization tract communicating with the prosthetic chamber; another clear criterion is the isolation of a bacterium from at least two distinct tissues or fluids harvested from the affected joint. In addition to the signs of certainty, there are tests which, if they occur in combination, may point to infection. These include an increase in the number of leukocytes in a sample or the presence of more than 5 leukocytes on the microscopic field, the isolation of bacteria from an affected area, an increased CRP value or an increased SVH, as well as the dominance of neutrophils in the aspirate and the presence of pus in the joint [65].

# 3. General considerations on preoperative screening

## 3.1. General

Significant improvements have reduced the rate of periprosthetic joint infection in recent decades, but nevertheless periprosthetic joint infection still remains the leading cause of revision after total knee and hip arthroplasty. Even though some risk factors such as demographic characteristics are rarely different, they allow more accurate expectations regarding individual risks of periprosthetic joint infection and thus are helpful for preoperative decision making. Others that increase the risk of periprosthetic joint infection but are potentially modifiable should be optimized before elective arthroplasty. With the increasing number of arthroplasties performed each year, the number of periprosthetic joint infections is expected to increase. Prevention is the first and best strategy to minimize this complication with sometimes devastating consequences. With recent emerging interests in prevention, several strategies have been described, but most emphasizing intraoperative and postoperative measures. Strategies to reduce periprosthetic joint infection should start from identifying and optimizing pre-existing risk factors. Understanding these risk factors helps to identify high-risk patients, and appropriate screening for pre-existing medical conditions is essential for developing appropriate interventions for those patients. Furthermore, these interventions should be integrated and in line with the general principles for surgical site infection. Although remarkable progress has taken

place in recent decades, many questions about standardized practice to prevent these complications remain unanswered for the time being [75].

## 3.2. Laboratory parameter aspects

Various studies have been carried out over the years on the use of biological parameters to determine early complications of total hip or total knee arthroplasty. The number of total hip arthroplasties is steadily increasing and with it the number of septic complications. At the same time the profile of bacterial resistance to antibiotics is changing, which is why prevention and early treatment of infections is important [77]. In order to establish the therapeutic attitude, it is important to diagnose as early as possible, so that in the first 4 weeks a conservative approach can be followed because the microorganisms are not yet organized in biofilms, while a late diagnosis, after more than 4 weeks, may require the need to remove the prosthesis because of the production of microbial biofilm resistant to antibiotic therapy and host defense mechanisms [78]. In medical practice, a number of tests are used as guidelines that may provide information about a possible inflammatory reaction.

The first-choice blood count is the hemoleukogram. This is a routine examination that can reveal changes in the erythrocyte, leukocyte and thrombocyte spheres by means of certain parameters. There are numerous studies in the literature on the role of inflammatory markers in the detection of periprosthetic infections. Currently, hema sedimentation rate and C-reactive protein are first-line screening tests for these infections due to their affordability and low cost, but their major drawback is their lack of specificity and sensitivity, which makes their use associated with false positive or false negative results. Recent studies have shown that the interleukin 6 level has a prognostic value comparable to that of C-reactive protein and in addition it has the advantage of being able to monitor the response to treatment of the patient with postoperative infection by normalizing at 48-72 hours, during which both C-reactive protein and heme sedimentation rate remain elevated. In 2016, Chen and colleagues studied the relationship between inflammatory response and postoperative complications following total hip arthroplasty in a prospective study of 148 patients in a prospective study in 2016, demonstrating a close relationship between increased levels of IL-6 and CRP and complication rates [79]. Falzarano analyzed the role of inflammatory markers and radiologic imaging investigations in screening for postoperative infections. The study was published in 2017 and followed 1248 patients. VSH, CRP and procalcitonin values were determined at 1 hour before surgery and postoperatively at 15 days and subsequently at 1, 3 ,6, 12, 24 and 36 months. Twenty-two cases of infection were identified. Inflammatory markers were positive in all of these cases, while radiologic changes characteristic of aseptic loosening of the endoprosthesis were absent in 6 of the cases [80].

### 3.2.1. Hematite sedimentation rate

The determination of HSV has a sensitivity of 91% and a specificity of 72% in the diagnosis of postoperative infections after hip fractures [82].

Shiha et al. noted that a normal serum HSV level does not exclude the possibility of the diagnosis of stent graft infection because its value may be influenced by prior systemic antibiotic therapy [83]. In the study carried out between 2009 and 2011 at the Isfahn treatment center, the SVH values of 45 patients who underwent total hip arthroplasty were analyzed. Its value was determined on

the day before surgery, on days 1, 2, 5 and 15 after surgery and later at 1, 3, 6 and 12 months respectively. There was an increasing trend in the first days, reaching a maximum on day 5, but then gradually decreased until returning to the normal value which was recorded at 3 months postoperatively. In patients with prosthesis infections, the SVH did not follow the normalization curve [80].

### 3.2.2. C-Reactive Protein

Specificity of circulating C-reactive protein is 68% and sensitivity is 92% [84]. Determination of CRP value in synovial fluid is considered superior having higher sensitivity and specificity than serum, but it is a more invasive method that cannot be easily repeated and is not routinely used for screening postoperative infections. In a study of 74 patients in which PRC variation was followed over 60 days, it was observed that PRC peaked on the third postoperative day and then decreased, returning to normal after about 3 weeks. Maintenance of an increased value after this interval was associated with infection at the arthroplasty site [85].

### 3.2.3. Fibrinogen

Klim et al. analyzed the sensitivity and specificity of fibrinogen in the detection of periprosthetic infections in a study with 84 participants, and they reported that its value was significant, with increased values associated with postoperative infections. At a fibrinogen value of 573 mg/dL the calculated sensitivity was 81% and specificity 75% [88].

The sensitivity, specificity, positive respectively negative predictive value and accuracy of inflammatory markers [89].

## 3.2.4. Other biomarkers

Another laboratory parameter useful in monitoring patients at risk of infection is procalcitonin. In the last 15 years it has become increasingly investigated as useful for the detection of sepsis [90]. It is a precursor of calcitonin and its level reflects the intensity of the systemic inflammatory response. Procalcitonin becomes detectable 2-4 hours after the triggering event and peaks at 12-24 hours. An increased level of this parameter is found in severe septic shock and is also used to determine postoperative septic complications or to assess the prognosis and clinical course of patients with severe infectious diseases. Several researchers have attempted to include procalcitonin in the list of serologic markers used in the early diagnosis of periprotic infection, but the specificity of this parameter was found to be insignificant in the studies performed [91].

Cytokines play an important role in triggering an effective immune response and are currently used in the early diagnosis of arthroplasty-associated infections. Cytokines, also known as interleukins, are protein-like substances that transmit signals necessary for the differentiation and proliferation of immune-competent cells. Thirteen molecular species are described in the literature, but of these, interleukin 6 and tumor necrosis factor-alpha are used in the early detection of hip and knee arthroplasty complications.

Interleukin 6 is a glycoprotein, with a molecular weight of 21 kDa, synthesized mainly by macrophages, but also by B and T lymphocytes, synovitis, chondrocytes, fibroblasts, endothelial and epithelial cells. It acts on a large number of cells and tissues by stimulating the humoral and cellular immune response through the differentiation and activation of B and T lymphocytes. Thus, interleukin production increases in viral or bacterial infections, inflammation or trauma, reaching detectable serum levels in a relatively short time. Special immunochemical methods are used to detect this parameter [92].

Tumor necrosis factor is a proinflammatory cytokine whose name derives from its ability to destroy tumor cells and induce hemorrhagic necrosis in transplanted mouse tumors. Two different molecular subpopulations, TNF alpha and TNF beta, are described.

TNF alpha is a protein with a molecular weight of 17 kDa synthesized by macrophages, lymphocytes, monocytes, neutrophils, keratinocytes and some tumor cells. It acts directly, through two receptors, causing conformational changes in the receptors that allow cascade activation of transcription of other proteins involved in cell proliferation, inflammatory response and cell apoptosis. Determination of serum levels of TNF alpha can be used to quantify the systemic inflammatory response. Serum determination of this cytokine is possible using immunochemical methods, and increases have been recorded in trauma, chronic inflammatory diseases as well as in autoimmune diseases [93].

### 3.2.5. Current status of inflammatory markers in relation to total hip and knee arthroplasty

The study by Kragsbjerg and co-workers in a group of 28 patients investigates changes in interleukin 6, tumor necrosis factor-alpha and tumor necrosis factor-alpha and C-reactive protein pre- and post-operatively for early diagnosis of infectious complications. Thus, the serum level of TNF-alpha was slightly altered in all patients, while the serum level of IL-6 reached a level above 100 pg/ml at 36 hours after surgery. The serum reactive protein level remained above 100 mg/ml for 106 hours after surgery, being the parameter with the longest half-life. In relation to the clinical and paraclinical changes, as well as the postoperative time period, IL-6 may represent a useful marker in the early diagnosis of periprosthetic infection [94].

Changes in interleukin 6 in patients who developed a periprosthetic infection as a complication of arthroplasty were also reported in the study by V. Mandalia et al. supporting the superior predictive value of this serologic marker. The change in interleukin 6 value starts within the first 6 to 12 hours post-surgery, and its normalization is achieved by 72 hours. The rapid increase and return to baseline value of interleukin 6 provides superiority of this parameter in contrast to C-reactive protein and hematiocyte sedimentation rate [95].

At present, studies are published in the literature, focusing in particular on post-operative variation in erythrocyte sedimentation rate and C-reactive protein (CRP) in order to diagnose possible arthroplasty-related complications early. Several studies have been carried out in different medical centers around the world, and one of the hypotheses put forward by researchers is the interaction between race, health status of the population, environmental factors and variation in serum

parameters. The results reported according to these studies demonstrated that the maximum value of C-reactive protein measured post-operatively was recorded at 48 hours, with a return to baseline occurring over the following weeks. The length of time that C-reactive protein was above normal is also influenced by the type of surgery. The CRP value in patients undergoing total knee arthroplasty was above normal for 60 days. The return to the normal value of this parameter was achieved within 21 days after total hip arthroplasty surgery.

In terms of the variation in erythrocyte sedimentation rate, the maximum was recorded on the fifth day post-operatively and the return to normal values was recorded at 90 days post-operatively. The study conducted by Jason White and colleagues in a group of 26 patients undergoing hip and knee arthroplasty showed that there were no significant differences in the variation of parameters in the postoperative control of the two types of surgery. Although total knee arthroplasty is considered a more traumatic procedure, no significant changes in C-reactive protein values were recorded in the present study [96].

Khalilolah Nazem et al. in their study attest to the importance of these two parameters in the early diagnosis of post hip or knee arthroplasty complications without any semi-significant differences in the SVH or CRP between the two types of intervention [97].

The authors of studies carried out over the years claim the benefit of early diagnosis of periprosthetic infection by knowing the curve of change of the two parameters in relation to the time and type of surgery.

Saleh and his collaborators highlight in their published article the use of the two parameters, HSV and CRP in the diagnosis of complications, especially periprosthetic infection. Thus, the sensitivity of HSV varies between 42% and 94% while the specificity ranges between 33% and 87%. PCR specificity varies between 20% and 100% and sensitivity between 72% and 94%. However, in the diagnosis of periprosthetic infection, imaging and microbiologic investigation methods should also be considered. Although synovial fluid examination is considered superior, the determination of serum changes of the biomarkers presented above is a less invasive option, which is why they are used as first line in screening for complications [98].

Obesity is considered a risk factor for complications in both hip and knee arthroplasty. Due to the associated proinflammatory state, higher postoperative cytokine levels have been recorded in the serum of overweight patients. Difficulties in the diagnosis of periprosthetic infection using leukocyte count, HSV and CRP have been recorded in patients with associated periprosthetic fractures, and therefore a collaboration with imaging and microbiologic examination is recommended.

The rate of infections after surgery is quite high according to some studies which rank this as the most feared complication with an incidence of 1-4% of all hip arthroplasties and 1-10% in total knee arthroplasty. Establishing an early therapeutic attitude is closely related to obtaining a diagnosis by minimally invasive methods in the shortest possible time.

Studies are currently underway to determine the superiority of D-dimers in the early diagnosis of complications. More research is being conducted both to determine the effectiveness of intracellular adhesion molecule 1 or lipopolysaccharide and the usefulness of flow-cytometric immunophenotyping

for the early diagnosis of complications associated with this procedure, particularly infectious complications [99].

# 4. General considerations on the prevention of periprotic infections

## 4.1. General

Prevention is the first and best strategy to decrease the risk of periprotic infections. With the emergence of interests in prevention, many treatises propose a number of strategies to minimize periprotic infections and should start by identifying and optimizing pre-existing risk factors [102]. Understanding these factors, can help identify patients at risk and appropriate screening for pre-existing medical conditions are essential for developing appropriate interventions for these patients. Specific demographic characteristics such as male gender and low socioeconomic status are associated with increased risk of periprosthetic infections. Women have a 17% lower risk of developing infection after hip arthroplasty compared to men. The presence of comorbidities such as congestive heart failure, chronic pulmonary disease, preoperative anemia, diabetes, depression, urinary tract infection, obesity, rheumatologic disease, metastatic tumors, valvular disease should be considered when performing hip arthroplasty. Adequate understanding of the patient's individual risk factors and proper application of general principles for preoperative optimization are paramount in reducing periprosthetic infections [103].

## 4.2. Urinary tract infection

Among the risk factors to be considered in periprotic infections is asymptomatic bacteriuria, which refers to the presence of bacteriuria without any signs or symptoms of urinary tract infection. Asymptomatic bacteriuria theoretically behaves as a potential reservoir of pathogens that increase patient mortality. The relationship between urinary tract infection and prostatitis infection was first described in 1970, however, the true existence of this relationship has become a controversial issue. Also, a variety of antibiotics are used in these conditions and a number of resistant bacteria have emerged worldwide [76].

Bacterial thrush screening before hip arthroplasty remains a controversial topic. The 2018 International Meeting on Orthopaedic Infections does not recommend preoperative urinary screening, whereas symptomatic urinary tract infections should be treated before hip arthroplasty [107].

The importance of determining asymptomatic bacteriuria is unclear. Some authors have proposed pyuria (more than 1000 white cells/ml) as a screening criterion for uroculture. Treatment should be considered before, during and/or after surgery with specific antibiotics according to the antibiogram, but arthroplasty should not be delayed in asymptomatic patients. Investigators recommend performing hip arthroplasty and treating patients with asymptomatic bacteriuria using empiric antibiotic therapy eight to ten days postoperatively, or with cefuroxime if preoperative pyuria is detected [108].

Many surgeons recommend screening and treating asymptomatic bacteriuria before total hip arthroplasty as standard protocol. The British Orthopaedic Association guidelines routinely recommend preoperative uroculture. Middle stream uroculture is the gold standard in the diagnosis of asymptomatic bacteriuria. However, uroculture is a time-consuming examination, around 24-48 hours to obtain the result. In addition, the cost of uroculture is higher compared to urinalysis. Urinalysis is a more affordable test that can be used to screen for many conditions. Given that there are many unnecessary urocultures that are required before total hip arthroplasty, the question arises as to when it is advisable to ask for urinalysis. Leukocyte esterase, nitrite, bacterial count and pyuria are some indications for urinalysis. Of these, the most specific and sensitive parameter is the bacterial count. Abnormal results of leukocyte esterase, nitrites, pyuria and bacterial count are associated with a higher risk of postoperative wound complications [109].

Antibiotics with a high urinary excretion rate are usually recommended in the treatment of urinary tract infections. For uncomplicated cystitis, nitrofurantoin and trimethoprim together with sulfamethoxazole are recommended as first line, usually given for three to seven days, depending on the severity. Elderly patients with pyelonephritis require parenteral antibiotic therapy. In this case fluoroquinolones, second or third generation cephalosporins or gentamicin are administered. Fluoroquinolones are the most commonly used antibiotics given in the outpatient setting and are also the most effective empiric antibiotics. Gentamicin is used in complicated urinary tract infections because it is active on many gram-negative germs.

## 4.3. Staphylococcus aureus infection

Staphylococcus aureus is the major pathogen implicated in orthopedic infections worldwide and approximately 20-30% of the general population are methicillin sensitive. The anterior nasal cavity is the main site of colonization. Throughout the literature it has been shown that patients who have bacteria in the commensal flora are at increased risk of infection in many clinical cases, including orthopedic patients. Nasal colonization with Staphylococcus aureus is a modifiable risk factor. More and more patients are undergoing preoperative screening and/or treatment protocols to reduce infection rates, including surgical procedures such as total hip arthroplasty. However the effectiveness and costs of these interventions have shown mixed results. Some studies have demonstrated a decrease in periprosthetic infection rate, while other studies have demonstrated no change in infection rate despite screening for and treating MSSA/MRSA [110].

## 4.4. Pre-operative prophylactic antibiotic administration

Some species of Propionibacterium acnes, Staphylococcus and Streptococcus on the skin surface involved in surgical infections are the first target of prophylactic antimicrobial treatment. The preoperative administration of prophylactic intravenous antibiotics preoperatively, prior to the performance of hip arthroplasty, to reduce their spread before incision is currently a widely used method. Cefazolin is one of the most commonly used antibiotics in many orthopaedic procedures. Clindamycin or vancomycin are recommended in patients allergic to penicillins, and vancomycin especially in those at risk of MRSA. These antibiotics should be given one hour before incision and continued twenty-four hours postoperatively. A duration of more than four hours or blood loss greater

than 1500 mL requires repeat antibiotic administration. With regard to Propionibacterium acnes, cefazolin appears to be an adequate antibiotic. Cephalosporins, semisynthetic penicillins and clindamycin are equally active on Propionibacterium acnes. Cephalothin, a first generation cephalosporin is currently the most active cephalosporin [113].

## 5. General considerations for the treatment of prosthetic infections

The gold standard for denture infection is a two-stage revision involving two surgical interventions. In the first stage, after microbiologic sampling, debridement and removal of dead or pathogen-affected tissues is performed and a spacer, which is actually a cement loaded with a high dose of antibiotic, is inserted into the remaining cavity, which will discharge the active substance. After a period of up to 4-6 weeks, the antibiotic is allowed to work, then patients are monitored for signs or symptoms of infection using clinical examination, inflammatory markers and sometimes aspiration of synovial fluid. Suspicion or persistent evidence of infection is treated by repeat debridement and antibiotic therapy. Once the infection has been resolved the second stage of prosthesis implantation is performed. The use of the spacer produces a high local concentration of antibiotics, much higher than that produced by systemic antibiotics, and can provide stability and better management of the space between the first and second stage of the procedure. The treatment failure rate was significantly lower among patients randomized to receive 3 months of oral antibiotics compared with those who received no other antibiotics after reimplantation [59].

To treat a periprotic infection correctly, rapid diagnosis is vital and should not be delayed under any circumstances. Consider some signs of certainty. One of them, and the clearest, is the appearance of a fistulization tract communicating with the prosthetic chamber; another is the isolation of bacteria from at least two distinct tissues or fluids collected from the affected joint. There are also tests which, in addition to signs of certainty, can confirm the presence of infection. These include an increased leukocyte count, the presence of more than 5 leukocytes/microscopic field, isolation of a bacterium from the affected area, an increased CRP value or increased HSV, as well as neutrophilia in the aspirate and pus in the affected joint.

Periprotic infection is often treated using prolonged courses of antibiotics and an effective screening program can be beneficial in preventing antibiotic resistance, but recolonization and resistance have proven to be a problem in institutions attempting to eradicate MRSA [114].

## 6. General considerations on the use of tranexamic acid

More and more studies lately have demonstrated the effectiveness of tranexamic acid used in total hip and knee arthroplasty. Intraoperative and postoperative bleeding has been shown to be significantly less with perioperative tranexamic acid. Patients needed blood transfusion much less often and the complication rate was much lower postoperatively.

A study published in September 2018 by Feng-Chih Kuo and associates demonstrated in a cohort of 930 patients a much lower transfusion requirement in patients in the group receiving tranexamic acid [115].

Another study published in March 2020 by Hamidreaza Yazdi and associates showed that the rate of infection in patients who received tranexamic acid is much lower than in those who did not. The study was done on a cohort of 6,340 patients of whom 3,683 received tranexamic acid and 2,657 patients did not. The complication rate in all patients was 16% anemia, 1.8% required postoperative blood transfusion and 2.4% developed postoperative infections, with a much lower rate of postoperative infections observed in patients who received tranexamic acid [116].

In August 2020, Mitchell R. Klement published a study in which he sought to demonstrate that the infection rate in patients undergoing revision total hip or total knee arthroplasty surgery was lower in patients who received tranexamic acid. The study was done on a group of 1,731 patients. The rate of infection in patients who received tranexamic acid was 3.30% while in patients who did not receive tranexamic acid it was 5.73% [117].

A retrospective study, published in May 2021 by Mount Sinai Hospital and the Icahn School of Medicine at Mount Sinai in New York, demonstrated that tranexamic acid poses no major risk in patients with a known personal pathologic history of coagulopathies or major heart attacks. The study was done on 765,000 patients.

Even the "American Association of Hip and Knee Surgeons" published a review study in which they analyzed the results of several studies published by Americans in the last 10 years and concluded that tranexamic acid decreases postoperative complications and the need for blood administration.

After multiple studies, which demonstrated the effectiveness of tranexamic acid in hip and knee arthroplasty, various studies began to appear to determine the most effective dose of tranexamic acid to be given to patients.

R. J. M. Morrison published a study in August 2017 demonstrating that a dose of 30 mg/kg body with a maximum of 2.5 g was superior to 15 mg/kg body with a maximum of 1.2 g. The study was done on a group of 1,914 total hip arthroplasties and 2,537 total knee arthroplasties [118].

In March 2020 Xiang-Dong Wu published a study comparing the administration of tranexamic acid as a single or multiple dose for 3 days. The study was done on 193 total hip arthroplasties and 166 total knee arthroplasties. It was found that in the multiple-dose group, hemoglobin levels decreased less than in the single-dose group. But there was no mention of need for comparative blood transfusion between the two groups [119].

In October 2017, Guang-lei Li published a study in which she meta-analyzed existing studies comparing the outcomes of taking tranexamic acid orally and taking it intravenously. They included 5 studies with 333 patients and concluded that taking tranexamic acid orally is more effective and patients in these groups needed fewer blood transfusions and did not experience such large decreases in hemoglobin [41].

Other studies such as: a March 2018 study, published in Orthopedicstoday, finds tranexamic acid to be highly effective in total hip and knee arthroplasty, but has not yet demonstrated the superiority of multiple doses over single doses, nor of oral versus intravenous administration.

"Guidelinecentral" also published an article in March 2022 stating that tranexamic acid administration in total hip and knee arthroplasties has a significant benefit, decreasing the number of blood transfusions and patients' hemoglobin does not decrease as much. But after their meta-analysis, they find that there are no differences in this depending on the dose given to patients or whether tranexamic acid was given orally or intravenously.

Kiyoshi Migita published a study in 2014 to compare the efficacy of two anticoagulants and to do this he performed postoperative Doppler ultrasound of the lower limbs in hip and knee arthroplasty patients. He determined the incidence of deep vein thrombosis to be approximately 24.3% in knee arthroplasty patients and 12.6% in hip arthroplasty patients [120].

The majority of the literature shows the efficacy of tranexamic acid when used to decrease intraoperative and postoperative bleeding. There are also articles that still consider that it should be administered with caution and with the informed consent of the patient before administration[121], [122].

# CHAPTER 2

## Personal contribution

## Main and secondary objectives of the thesis

## Main objectives:

1) To understand and know in detail the changes in inflammatory samples after hip and knee arthroplasty, in order to facilitate early detection of peri-prosthetic infections.
2) To establish the correlation between untreated asymptomatic infections and peri-prosthetic infections after hip and knee arthroplasty.
3) To determine the risk of deep vein thrombosis and pulmonary thromboembolism depending on the dose of tranexamic acid administered to patients undergoing total hip and knee arthroplasty.

## Secondary objectives:

1) Analysis of changes in inflammatory samples in patients who developed peri-prosthetic infection after hip and knee arthroplasty.
2) Determination of the most common pathogens that are encountered in peri-prosthetic infections after hip and knee arthroplasty.
3) Analysis of the most common asymptomatic infections and their resistance to treatment.
4) To establish whether there is a difference in the decrease in hemoglobin level according to the dose of tranexamic acid administered to patients undergoing total hip and knee arthroplasty.

# General research methodology. Ethical considerations.

The studies were conducted between January 2016 and December 2022 and were approved by the "Ethics, Medical Deontology and Discipline Commission of the Sibiu County Emergency Hospital" (protocol number 29083/8 December 2023). All the studies conducted in the present research included patients who underwent total hip and knee joint arthroplasty, who were hospitalized in the Orthopedics and Traumatology Clinic of the Sibiu County Emergency Hospital. All studies were carried out on the basis of a protocol in accordance with national and international requirements for medical research on human subjects and strictly adhered to the principles stipulated in the Declaration of Helsinki. All patients included in the studies in this research signed an informed consent. Prior to signing the informed consent, all patients were informed of the terms of the studies, the conditions for withdrawal from the study and were assured of the confidentiality of the data provided.

For each study included in this research, a research protocol was established and certain steps were followed, as follows:

1) Inclusion of patients in research groups, according to the inclusion criteria established for each study.
2) Determination of demographic data, personal pathological history of the patients included in the study (data obtained by anamnesis or from the observation sheet).
3) Collecting biological samples and performing Doppler ultrasound of the lower limbs (in the case of study 3), according to established protocols.
4) Postoperative follow-up of patients, according to established protocols.

The specific methodology as well as the specific inclusion/exclusion criteria are described in detail in each of the studies conducted.

# Study I

## 1.1. Working hypothesis

The objective of this work is to monitor post-operatively the variation of C-reactive protein, fibrinogen and hema sedimentation rate in order to obtain additional information that may benefit the patient in the early diagnosis and treatment of infectious complications and to influence hospitalization costs.

This research aims to answer the question that is increasingly being asked in the literature as to whether careful monitoring of acute-phase proteins in the postoperative period can detect periprosthetic infection early.

Summarizing the working hypothesis for this study, the following hypotheses were formulated:

1. It is considered necessary to know the normal variation of these markers and the time to return to normal depending on the type of surgery.
2. The importance of careful monitoring of these three parameters for early diagnosis of complications associated with hip or knee arthroplasty is described.

## 1.2. Aim and objectives

The main aim of this paper is to demonstrate the usefulness of monitoring biological parameters in medical practice in order to early diagnose infectious complications after hip or knee arthroplasty.

The overall objective of this work is to evaluate certain biological parameters and their variation in the selected group of patients, which will lead to the development of a conclusion on their usefulness in the early diagnosis of infectious complications.

The specific objectives that will direct the study towards demonstrating the hypotheses presented above are:

- Analysis of the patient's clinical-evolutive features.
- Analysis of paraclinical data and their normal variation in relation to patient's age and gender.
- Evaluation, interpretation and analysis of changes in the group of patients studied.

## 1.3. Materials and methods

The participants in this study were selected from among patients treated by hip or knee joint arthroplasty surgery and who were subsequently followed postoperatively at the Orthopedic and Traumatology Clinic of the Sibiu County Emergency Hospital.

The study focused on following the biological evolution of patients in three stages until discharge.

- Pre-operative stage
- Post-operative stage
- Patient discharge

Clinical and paraclinical evaluation of patients was performed in these three stages in order to monitor their evolution and to catch early possible complications associated with the intervention.

The patient's evolution has taken into account possible complications such as

- Early infections
- Late infections

Participants were included in the study on the basis of compliance with inclusion and exclusion criteria.

The inclusion criteria for patients in this study were:

- Subjects hospitalized and treated in the Orthopedics and Traumatology Clinic of the Sibiu County Emergency Hospital.
- Patients who have had total hip or knee replacement

Patient exclusion criteria in this study were:

- Patients with altered parameters due to other comorbidities

## 1.4. Results

### 1.4.1. Results obtained on a group of patients without infections

As a first step, we checked the baseline achieved in our patient groups. To achieve this, we analyzed data from 31 patients, who received total endoprosthesis of the coxo-femoral joint or knee joint in the Orthopedics and Traumatology Clinic of the County Emergency Hospital Sibiu. These patients were operated between May 1, 2018 and August 31, 2018 [123].

Of the 31 surgeries performed during the study period, 11 were knee arthroplasties, constituting 35% of all surgeries, while 65% of the surgeries performed were total hip joint arthroplasties.

The data analyzed included a pre-operative phase, in which the initial hemoglobin values were measured, as well as the inflammatory parameters, represented by C-reactive protein, hema sedimentation rate, and fibrinogen. Subsequently, in the postoperative phase, emphasis was placed on the variation of these parameters and their usefulness in early detection of possible infectious complications.

One of the parameters assessed both pre-operatively and postoperatively was the hemoglobin level. The normal reference values for this parameter ranged from 12.1-16 g/dL with small variations depending on the age and gender of the patient. Analysis of the data showed that 19% of the patients

included in this study had a pre-operative hemoglobin level between 8-12 g/dL. We consider the hemoglobin value below 7g/dL as a prerequisite for the classification of patients with severe acute anemia requiring treatment.

As reported in the general part of this paper, the inflammatory parameters C-reactive protein, fibrinogen and erythrocyte sedimentation rate are monitored in order to diagnose early complications associated with these types of orthopedic procedures.

In the group of patients with hip joint endoprosthesis no postoperative complications were recorded.

In this paper we will analyze the variation of each parameter in the postoperative period, depending on the surgery performed.

The normal reference values in this study were for C-reactive protein less than 5, while the ESR value was considered normal if it was below 20 mm/h for males and below 30 mm/h for females. The third inflammatory marker assessed by this study had normal reference values between 200 and 400 mg/dl. Any increase above the above values was carefully analyzed, both in the operative setting and afterwards, as a possible complication.

A graphical representation of the post-operative variation of C-reactive protein in patients who underwent total hip joint arthroplasty shows an increase in this parameter starting from the first day after surgery. Its values continue to increase, reaching the maximum value on the third and fourth postoperative day respectively. The return to the initial value is gradual. In the studied group, the normal value was completely reached 21 days after surgery.

The evolution of the C-reactive protein in the second batch examined showed an increase in this parameter from the first day after the surgical procedure, and its value continued to increase until the third day, when the maximum value was reached. The return to the normal reference value is also gradual in this case, with a halving on the seventh day.

Comparing the data obtained for the VSH variation in the two groups, i.e. hip arthroplasty and knee arthroplasty, a difference can be observed in the normalization trend of this parameter, being slower in the group of patients who underwent total knee arthroplasty. As regards the variation of this parameter, a similarity can be observed between the two groups. The maximum value was reached in both groups on the third postoperative day, but in the second group the hema sedimentation rate was higher. The normalization of this parameter starts after the third day. In the first batch in this stage no changes were recorded, while in the second batch significantly increased values of the SVH were recorded even on the seventh day, despite the decreasing trend. All data presented are illustrated in Figure 10.

The last parameter studied in this paper is fibrinogen. This glycoprotein synthesized in the liver belongs to the group of acute-phase proteins, and an increase in the serum level of this parameter was recorded in the first 12-24 hours after the inflammatory reaction. In this work, its normal value was considered to be between 200 and 400 mg/dl.

There is a slight increase towards the upper limit of the normal value of this parameter in the first hours after surgery, with the tendency to increase maintained for the 3rd and 4th day after

surgery. An isolated case can be noted in which the increase on the first day reached double the normal value. The maximum value measured for this parameter was recorded on day 4 in a male patient, without an associated infectious clinical context. Normalization of this marker of inflammation occurs gradually, remaining above normal values even on day 5 post-intervention.

### 1.4.2. Results obtained on a group of patients with periprotic infections

A complication frequently associated with the two surgical procedures analyzed in this study is infection. The infection rate after total hip joint arthroplasty reaches an incidence of 1-4%, according to studies published in the literature. Studies looking at the rate of infection after knee arthroplasty have specified that it is between 1% and 10%. In the analysis of the two groups, infectious complications were recorded in the second group of patients, total knee arthroplasty.

In the second part of this prospective study, the data of 62 patients who underwent hip or knee joint prosthesis at the Orthopedics and Traumatology Clinic of the Sibiu County Emergency Hospital were analyzed.

The prospective study group consisted of patients who underwent total or partial hip joint arthroplasty and total knee arthroplasty at the Orthopedics and Traumatology Department of the Sibiu County Emergency Hospital, in the period 2016-2022 and in whom a superficial or deep postoperative infection was identified up to the prosthesis room.

Infections were detected in 62 patients out of a total of 4076 coxofemoral joint and knee arthroplasties performed at the Orthopedics and Traumatology Department of the Sibiu County Emergency Hospital in the period 2016-2022 [123].

Out of the group of patients who underwent hip joint arthroplasty, 28 patients underwent total hip arthroplasty based on the diagnosis of coxarthrosis and 14 patients underwent hip arthroplasty based on the diagnosis of femoral neck fracture. In patients who underwent hip arthroplasty based on the diagnosis of femoral neck fracture, 10 underwent total hip arthroplasty and 4 underwent partial hip arthroplasty.

In terms of ESV and fibrinogen, no significant changes were identified that could signal potential infection. Variations in CRP levels showed deviations from the ex-pected norm in this analysis. Therefore, we decided to focus only on variations in postoperative CRP values.

Compared to these average values obtained in this standard group, in our group of patients with postoperative infections we obtained the following values.

| Day | Day 1 | Day 3 | Day 6 |
|---|---|---|---|
| THA | 93.4136 | 115.4141 | 84.8823 |
| TKA | 56.5542 | 98.1642 | 79.0108 |

**Tabel I.** CRP values after THA and TKA in patients with infection.

The observed changes showed distinct patterns depending on the type of prosthesis implanted. Accordingly, we stratified patients into two groups: those undergoing hip arthroplasty and those undergoing total knee arthroplasty.

In the context of hip arthroplasty patients, the observed changes were not readily apparent. On the first postoperative day, the changes were within normal limits, with the maximum value being reached on the third day. However, in both chronic and acute cases, the values on day six did not show the anticipated decrease. The baseline value from our previous data set and the literature suggests an expected range of approximately 20-30 mg/L, with a mean of 26.35 mg/L at day six on our previous date. In the group with infections, values of about 40-50 mg/L were observed, and in some isolated cases of acute infection, values even exceeded 100 mg/L.

In all patients with acute infections after total hip arthroplasty, even twenty-one days after surgery, persistently elevated CRP values above the reference range were evident. The majority had CRP values above baseline on day six, with cases reaching 30.99 mg/L, 82.79 mg/L, and in extreme cases 364.85 mg/L or 167.70 mg/L. A subset of five patients had slightly lower values, hovering around 15 mg/L, although still elevated compared to the normal range at this postoperative interval. In contrast, in patients with chronic infections after total hip arthroplasty, no substantial changes were observed at 21 days postoperatively, all of whom maintained CRP values close to preoperative levels.

The difference between CRP values in acute and chronic infections are about the same between acute and chronic infections on days 1 and 3, which means that we have about the same increase in both groups. The difference between the groups on day 6 is much larger than before, showing a slower decrease in CRP in the acute infection.

Following an acute infection after PTG, noticeable changes are apparent from the first postoperative day. In patients with acute infection, the value on the first postoperative day is significantly lower than the standard observed both in our reference group and in the literature. The mean value on the first postoperative day, usually around 80 mg/L, contrasts with our observed mean of around 35 mg/L, with all patients falling in the range 30-40 mg/L.

For patients with chronic infections, substantial changes are less evident. Only one case shows a value of 141.72 mg/L on the first postoperative day, significantly higher than the normal range, and another case shows a value of 24.12 mg/L, considerably lower than the standard. Thereafter, there is an increase that peaks on days two and three, although these values are lower in patients with acute infections compared to typical levels on these days. Our reference value from previous data was approximately 108 mg/L, consistent with values found in the literature. In patients with ongoing infections, mean CRP values range from 60-75 mg/L.

On the third postoperative day, patients with chronic infections show minimal changes. In the case with a value of 141.72 mg/L, this increases only marginally to 155.56 mg/L. On day 6, both acute and chronic infection groups approach the normal baseline, which in our cohort was 65 mg/L. A significant deviation from normal occurs in the chronic infection with a postoperative CRP value of 24.12 mg/L, which shows only 9.48 mg/L at this time. On day 21, minimal changes are seen with values close to the normal range.

The difference in CRP values between chronically and acutely infected patients is quite high from day 1, on days 3 and 6 they are higher, but higher for chronic infections. Only around day 21 the difference starts to be smaller, but still higher for chronic infections.

The pathogens identified in these patients showed considerable diversity. Staphy-lococcus aureus was the most prevalent, identified in twenty-eight patients. Of these, three patients had a form of Staphylococcus aureus with no resistance to any antibiotic, while the remainder either initially had antibiotic-resistant forms or developed resistance during treatment. In particular, one patient showed resistance to penicillin, and another showed multiple resistance to cefoxitin, clindamycin, erythromycin, oxacillin, penicillin and tetracycline.

In addition to Staphylococcus aureus, various staphylococci were also identified in these patients, including Haemolyticus (6 cases), Epidermidis (6 cases), Hominis (8 cases), Warneri (2 cases) and Lugdunensis (1 case).

Other microbial infections included Enterobacter cloacae (4 cases), Enterococcus (4 cases), Enterococcus faecalis (14 cases), Escherichia coli (10 cases), Pseudomonas aeruginosa (12 cases), Acinetobacter baumannii (4 cases), Enterobacter (8 cases), Proteus (6 cases), Morganella morganii (1 case), Klebsiella (10 cases), Aerococcus viridans (2 cases), Proteus mirabilis (1 case) and Serratia marcescens (1 case).

Of the total cohort of patients, twenty-four individuals had infections caused by a single pathogen, while the remaining cases had combinations of two, three or, in isolated cases, even four pathogens during treatment. This complexity required frequent adjustments of the antibiotic regimen, guided by the latest antibiogram results. For example, of the twenty-eight patients infected with Staphylococcus aureus, only two had exclusive infections with this microorganism, while the majority had concomitant infections. The distribution of microbial diversity was fairly constant between patients with acute and chronic infections, with a remarkable proportion of cases of chronic infections with single microbial identification.

In the entire cohort, a single case occurred after PTG in which infection remained unresponsive to treatment efforts [124].

### 1.4.3. Case presentation

Case presentation: a brief presentation of a patient who presented with a PTG infection that did not respond to treatment and was left with chronic osteomyelitis.

We present the case of a 66-year-old female patient with a body mass index (BMI) of 46.71 (w: 121kg, h: 1.61m). From the personal pathologic history we note only hypertension under treatment. In November 2016 total knee arthroplasty was performed.

1.5 years after the operation, the patient has pain in the operated knee. After 2 years she presents to the medical rehabilitation ward. A control X-ray is performed where a periprosthetic fracture, a compression fracture of the tibia, a displaced tibial greater tuberosity fracture and the patient is transferred to the orthopedic department for specialized treatment.

Laboratory tests show elevated inflammatory samples (fibrinogen 681mg/dL, CRP 45mg/dL, VSH 91mm/h), local examination shows signs of infection (edema, erythema, warmth and pain). The therapeutic indication was reviewed in two stages. The prosthesis is extracted, the femoral component is well fixed and the tibial component is gently removed. The anterior tibial tuberosity fracture is examined, where friable, avascular bone is identified, which is removed and a Spacer is fixed with antibiotic. Ligamentous stability is checked and a decision is made to fit an external fixator. During the operation, a bacteriologic examination of 6 areas of the knee is performed and Proteus and Staphylococcus aureus infection is found. We administered Ceftazidimum 1grx2fl/day for 14 days during hospitalization and 4 weeks of Levofloxacinum 500mg 2tab/day and Sulfamethoxazolum + Trimethoprimum 400mg/80mg 2x2tab/day at home.

A CT scan is performed at 3 months and inflammatory samples are taken to determine the next therapeutic course. The external fixator is removed, clinical examination reveals further ligamentous instability and the patient is unable to perform knee extension. A decrease in inflammatory samples is observed, but not within normal limits (fibrinogen 410mg/dL, CRP 6.6mg/dL and ESR 26mm/h).

At 6 months after the first stage of revision, the inflammatory markers normalize (fibrinogen 389mg/dL, CRP 2.99mg/dL and VSH 19mm/h) and the local examination is normal. Due to lack of tibial tuberosity and ligamentous instability, the decision is made to perform a knee arthrodesis with a CM rod, and a bone graft is prepared from the bone bank to fill the bone defect.

Three years after knee arthrodesis, the patient presented to the outpatient clinic with superinfected varicose ulcers and a fistula in the knee communicating with the arthrodesis site. The patient had been to a dermatology consultation and general surgery consultation for varicose ulcers in the past year, where she received treatment for these ulcers and was advised to see an orthopedic specialist, but she did not follow the indications.

A bacteriologic examination is performed and reveals an infection with Morganella morganii. The patient refuses hospitalization and is treated at home with Ceftazidimum 1grx2fl/day for 21 days without success. After 6 months she is admitted to the orthopedic ward. On admission, a bacteriologic examination with antibiogram is performed again, which reconfirms Morganella infection. Inflammatory tests are elevated (CRP 49.6 mg/dL, fibrinogen 668.4 mg/dL and VSH 76mm/h). Proceed with arthrodesis rod removal, debridement, chemical and mechanical toilettage and antibiotic treatment [125]. In the first phase, treatment with Ceftazidimum 1grx2fl/day for 2 weeks is started unsuccessfully, then Amikacinum 500mg/2gr 2fl/day is added for another 2 weeks. During this period weekly bacteriologic examination and antibiogram were performed. On antibiogram performed 4 weeks after admission it was found that the germ had become resistant to Ceftazidinum. Ceftazidinum was

replaced with Meropenem 1gr/day and treatment was continued for 2 months without success. Then Piperacillinum + Tazobactamum 4g/0.5g 2fl/day and Amikacinum 500mg/2ml 2fl/day 2fl/day for 1 week, then Piperacillinum + Tazobactamum was again replaced with Piperacillinum 4g/0.5g for 2 weeks. All antibiotic therapies were administered on the basis of antibiogram and after consultation with the infectious disease physician.

After antibiotic treatment and repeated chemical and mechanical dressings, the wound closes. On discharge, inflammatory samples were still above normal CRP 14.1 fibrinogen 558.0 and ESR 92. The patient was discharged with the wound healed.

## 1.5. Discussions

The main objective of this paper was to demonstrate the usefulness of monitoring biomarkers, represented by hemacyte sedimentation rate, C-reactive protein and fibrinogen, in the postoperative period of total hip and knee arthroplasty. This was achieved by integrating the data obtained from the individual form, the statistical analysis performed in the previous chapter and the interpretation of the results found in the previous chapter.

This work followed the variation of biological parameters in the postoperative period, namely the time required to normalize the values of the three parameters studied. Thus, knowing these data, it was possible to answer the second question of this study, namely the benefit of these parameters in the early diagnosis of periprosthetic infection.

In the results of the infection-free group of this study, it can be observed the rapid upward trend of C-reactive protein, hematiocyte sedimentation rate and fibrinogen from the first 24 hours after the intervention. Making a correlation with data from the literature and the present study, it can be observed that the maximum value for C-reactive protein was recorded on the third day, while in some studies it is recorded in the first 48 hours, with complete normalization between 14 and 42 days respectively. In the present study, the decrease of this parameter towards the reference value is evidenced, which is reached by day 21 if no complications are present. From the literature it is known that the maximum value reached by the SVH after an orthopaedic intervention is on the fifth day, and the slow normalization trend of this parameter makes it possible to return to normal limits 90 days after the intervention. Probing this hypothesis, we can exemplify by analyzing the data of this study that the maximum value of the SVH was recorded on the fifth day, with increased values also recorded at discharge, and in the patients evaluated on day 21, values slightly above the reference value were also recorded. In this study the variation of fibrinogen was followed, thus it was found that this traumatic marker increases in the first hours after the injury, reaches the maximum value on the third and fourth day respectively, and tends to return to baseline value in the first week after the intervention. There were minimal semi-significant differences in fibrinogen values between the two groups. A more pronounced increase in fibrinogen was observed in the first group of patients, the hip arthroplasty group, while the normalization of this parameter was influenced by associated complications in the second group of patients studied. Statistical analysis showed no significant differences in hemoglobin values.

In the results of the infection-free group, minimal semi-significant differences can be observed between the two groups of patients in terms of the slower normalization trend of the studied parameters in the group of patients who underwent total knee arthroplasty. This may be explained by the complications associated with this group.

C-reactive protein (CRP) has been shown to be of crucial importance in the evaluation of perioperative infections in patients undergoing total hip and total knee arthroplasty. In our study, it was observed that CRP levels were significantly higher in patients with infections compared to those without complications. This increase is an early indicator of the inflammatory process and is essential for prompt diagnosis and treatment of infections.

Compared with other inflammatory markers, CRP has been shown to be a more rapid and reliable indicator of infection, providing clinicians with a valuable tool for early intervention. This is supported by research by Ghanem et al, who showed that CRP levels rise rapidly in the presence of infection and decrease significantly with effective treatment.

In the context of infection after PTSS, the CRP value becomes particularly significant for acute infection. A notable increase in CRP above normal levels is observed on the sixth day after surgery. The CRP levels are four times higher than normal, with values of approximately 111 mg/L, which should be approximately 26.35 mg/L. The values obtained in this group of patients are higher than in other similar studies in the literature [126].

In chronic infection, levels are slightly higher, but not statistically significant.

After PTG, CRP levels in acute infection showed an intriguing pattern. Despite the presumed increase in CRP values in case of infection, these values persist below baseline values. CRP levels on day 1 and day 3 after surgery are lower than expected, with a value of only 38 mg/L on day 1 and only 71mg/L on day 3. This result is different from other studies in the literature that showed an increase in the number of patients with acute infection after PTG [65].

In chronic infection, levels are higher, but similar to the increase after PTG [127].

The high prevalence of Staphylococcus aureus, a ubiquitous bacterium, highlights the need to address its potential impact on surgical site infections [67]. However, the fact that only a small proportion (10.71%) had a nonresistant form of Staphylococcus aureus, raises concerns as antibiotic resistant strains can significantly complicate treatment strategies.

A significant percentage (61.29%) of patients presenting with multiple germ infections emphasizes the complex nature and complexity of the management of these cases. The identification of 19 different pathogens in infection cases highlights the great diversity of microorganisms contributing to these infections. This diversity requires customized treatment plans and the ability to adapt strategies to emerging pathogens.

The strength of the study is that we followed the inflammatory samples over a long period of time and in a fairly large sample.

Limitations of the study are that it is a retrospective study, the number of patients enrolled in the study is small, we are not sure if all infected patients have returned to our hospital and there are several types of procedures.

## 1.6. Conclusions

In conclusion it is noted that C-reactive protein remains a fundamental biological element in the biological evaluation of infectious complications, but needs to be complemented with other tests with higher specificity for the diagnosis and further treatment of periprostetic infections.

The results of the study show that postoperative CRP values in patients with joint infection after SST and PTG show higher values for SST and lower values for PTG [123].

# Study II

## 2.1. INTRODUCTION

Significant improvements have reduced the rate of periprosthetic joint infection in recent decades, but periprosthetic joint infection still remains the leading cause of revision after knee and hip arthroplasty. Even though some risk factors such as demographic characteristics are rarely changeable, they allow more accurate expectations regarding the individual risks of periprosthetic joint infection and thus are helpful for preoperative decision making. Others, which increase the risk of periprosthetic joint infection but are potentially modifiable, should be optimized before elective arthroplasty. With the increasing number of arthroplasties performed each year, a corresponding increase in the number of periprosthetic joint infections is also expected. Prevention is the first and best strategy to minimize this complication with sometimes devastating consequences. Concurrent with recent emerging interests in prevention, several strategies have been described, but most emphasize intraoperative and postoperative measures. Strategies to reduce periprosthetic joint infection should begin with the identification and optimization of pre-existing risk factors. Understanding these risk factors can help to identify patients at increased risk, and appropriate screening for pre-existing medical conditions is essential for developing appropriate interventions for these patients. Furthermore, these interventions should be integrated and in accordance with general principles for surgical local infection. Although remarkable progress has been made over the past decades, many questions regarding standardized practice to prevent these complications remain unanswered for the time being [57].

It is essential to check whether the patient has other concomitant local or distant infections, such as urinary tract infection, and those with concomitant infections should be optimized by eradicating the infection prior to elective arthroplasty with appropriate antibiotic treatment. The same principle will apply to patients with preoperatively detected infections found preoperatively in nasal exudate, dental infectious foci, or groin plica, which also require treatment before surgery [58].

## 2.2. Aim and objectives

The present study aims to analyze preoperative infections in patients undergoing hip and knee replacement surgery. Over time, the multiple benefits of preoperative screening for the preoperative detection and treatment of associated infections have been demonstrated, leading to a reduction in intraoperative and postoperative complications.

This paper aims to analyze the knee and hip arthroplasty surgeries of patients in the Orthopedic Department of the Sibiu County Emergency Hospital. This study aims to emphasize the importance of preoperative detection of associated infections, mainly asymptomatic, and their preoperative treatment. At the present time it is considered necessary to emphasize the positive results due to their detection and appropriate treatment, being an important element in the longevity of arthroplasty. It is also important to highlight the category or categories in which preoperative infections are most frequently positive, so as not to miss any preoperative infection in the category/categories in which the infection is most frequently present.

The determination of the pathogen that caused the positive infection together with the related examination is a main objective of this paper and one of the "raw materials" of this study. It is considered essential to also examine which is the most common preoperative examination leading to positive results in females and males, respectively.

The detection of multi-drug resistant bacteria is also one of the objectives of this study, which is particularly important for choosing the appropriate treatment so that it is effective.

## 2.3. MATERIALS AND METHODS

In the first phase of the present study, a retrospective analysis of 46 patients hospitalized in the Orthopedic Clinic Section of the Sibiu County Emergency Hospital who underwent hip or knee arthroplasty and were tested preoperatively for concomitant infections was performed.

The necessary data were retrieved and analyzed from clinical observation sheets:

- Personal data: background, gender, age, occupation
- Presence or absence of infection
- Incriminated pathogen
- The examination that led to the positive results
- Response to treatment
- Multi-resistant bacteria

Patient inclusion criteria for this study are as follows:

- Patients hospitalized and treated in the Orthopedics and Traumatology Clinical Department of the Sibiu County Emergency Hospital.
- Patients diagnosed with periprotic infection

## 2.4. Results

After analyzing the observation sheets and studying clinical and paraclinical parameters, it was decided to divide the patients as follows:

### 2.4.1. Presence or absence of preoperative infections

Patients who underwent surgery for hip or knee arthroplasty with or without preoperative infections on admission for surgery.

Pre-operative examinations detected 16 asymptomatic infections among patients undergoing hip and knee surgery out of a total of 46 patients screened, which represents one third of all patients. This result should be taken into account considering that the percentage of 34% is considerable, 1 out of 3 patients presenting with asymptomatic infections at hospital presentation.

### 2.4.2. Pathogen involved

Patients who presented with infections detected at preoperative examinations were divided according to the pathogen involved.

The results show a significant discrepancy in favor of Escherichia Coli bacteria which is present in almost 90% of cases compared to staphylococcus which is present in 12% of cases.

### 2.4.3. After the examination detecting the pathogen involved

The examined patients were divided according to the pathogen involved in relation to the examination that gave the positive result.

It can be seen that the greatest success in terms of detecting asymptomatic preoperative infections is represented by the uroculture, which yielded 12 positive results out of a total of 16, i.e. a significant percentage of 75%. On the other hand, all positive results detected on urine culture were positive for E. coli bacteria, without detecting other incriminated bacteria. Looking at the pharyngeal exudate examinations it can be stated that 4 positive results were detected out of the total of 16, only one fourth of the total positive results, but unlike uroculture, using pharyngeal exudate both E coli and Staphylococcus were detected equally, respectively 2 positive results for E.coli and 2 for Staphylococcus.

### 2.4.4. Presence of multi-resistant bacteria

Subjects were divided according to the presence or absence of infection, respectively, according to treatment resistance.

Out of the total number of patients, a considerable percentage of patients have no preoperatively detected infections (65%), but a third of them have asymptomatic infections (35%), 22% have infections without resistance to treatment and a significant 13% have infections with multi-drug resistant bacteria.

### 2.4.5. Treatment response of patients detected with preoperative infections

Selected patients were categorized according to treatment response and the pathogen that caused the infection to be positive.

In this figure it can be seen that uroculture determined the highest percentage of positive results determined by the preoperative examinations, detecting totally E.coli, with a 100% response to treatment. The pharyngeal exudate, detecting half E.coli and half Staphylococcus, also shows the highest percentage in treatment response, resulting from the two investigations a 100% treatment response percentage. By following figure 7 it can be seen that 13% of the total infections are multidrug resistant infections, respectively 4 in urine culture and 2 in pharyngeal exudate, but in figure 8 it can be seen that although multidrug resistant, the response to treatment is favorable in all cases.

## 2.5. Discussions

The presence of asymptomatic preoperative infections means that both patients and medical staff do not suspect the presence of these infections, which statistically are found to be numerous enough to pose problems for some patients, especially those with multi-drug resistant bacteria.

The statistical results show a percentage of 34% asymptomatic preoperative infections in patients presenting for hip and knee replacement surgery, which means that 1 in 3 patients presenting for arthroplasty surgery has an associated asymptomatic infection that needs to be treated so as not to spread the pathogen to a periprosthetic infection.

As regards the pathogen incriminated, this study shows that Escherichia coli bacteria are almost exclusively present, with a massive 87.5%. The difference in percentage is obtained by Staphylococcus, with a percentage of 12.5%. The results show that when the patient presents for surgery, patients presenting with an associated asymptomatic infection have a very high probability that the pathogen involved is Escherichia Coli.

Analyzing from both the examination that detected the pathogen and the pathogen incriminated, it results that uroculture determined three quarters of all detected asymptomatic infections. What is noteworthy is that although uroculture detected three quarters of the total infections, it detected exclusively Escherichia coli, without detecting other incriminating bacteria. Looking at the pharyngeal exudate, although it yielded only a quarter of the total positive results, it can be concluded that it detected both Escherichia coli and Staphylococcus bacteria.

Multidrug-resistant bacteria are an issue to be considered for preoperative asymptomatic infections, in this study it was found that out of the total selected patients, 13% of them had infection with a multidrug-resistant bacteria. This has to be taken into account because the appropriate treatment has to be selected so that it is effective for the multi-drug resistant bacteria.

The pathogen determined by preoperative examinations showing multi-resistance is present in 67% of cases by Escherichia Coli, and the remaining percentage is represented by Staphylococcus.

About the response to treatment in preoperative asymptomatic infections the statistical data show encouraging results because uroculture, determining most of the preoperative positive results, detecting exclusively Escherichia coli, has the maximum percentage of response to treatment. The pharyngeal exudate also shows results of 100% response to treatment, although it detected half Escherichia Coli and half Staphylococcus. It should be noted that infections with multi-drug resistant bacteria are also included in this maximum treatment response statistic.

Calculating first for each gender and then comparing the sexes we get a result of 30% male patients presenting with asymptomatic presentation-associated infection, and for females a higher percentage of 38%, this difference being a notable and expected one due to female anatomical and physiological specificities, mainly due to the shorter urethra than men.

Pre-operative screening is of immense value in adequately preparing patients for HSCT and PTG. By collecting specimens for urinary tract infections, pharyngeal exudate, and inguinal envelopes, surgeons can assess the patient's overall health and identify potential sources of infection. This proactive screening approach serves to minimize the risk of postoperative infections, helping to ensure that patients are in optimal condition for the impending surgical procedure. These confirm other studies in the literature [128].

## 2.6. Conclusions

Thus, we can conclude that the current study confirms the data demonstrated by other studies in the literature that have shown a benefit in the diagnosis, treatment of preoperative asymptomatic infections and reduction of the risk of postoperative infectious complications.

The preoperative detection of asymptomatic infections is significantly related to periprotic infections. In the group of patients, with hip arthroplasty after femoral neck fracture, 85% of those who developed a periprosthetic infection had an asymptomatic infection preoperatively. However, the pathogens identified preoperatively were identical to those responsible for periprosthetic infections in 50% of cases [123].

# Study III

## 3. 1. Introduction

Tranexamic acid ( TXA) is a synthetic acid that limits blood loss by inhibiting fibrinolysis and thrombus degradation. TXA reversibly saturates the lysine-binding site in the plasminogen, thereby preventing the interaction of the active protein, plasmin, with the binding site on the fibrin surface, inhibiting the degradation of fibrin by plasmin. Tranexamic acid (TXA) is available in numerous intravenous (IV), topical and oral forms and is widely used in various surgical specialties.

A recent study shows that using tranexamic acid can greatly reduce the need for blood transfusions.

Data on perioperative outcomes, particularly those related to thromboembolic and renal events, which are often the main concern with the use of antifibrinolytic agents, are scarce. Even more so are no population-based data detailing outcomes in a large cohort outside randomized controlled trials, which often include only patients selected on the basis of strict inclusion criteria, which practically do not reflect real-world practice outcomes and are burdened by low external validity.

IV and topical administration of tranexamic acid appears to be more effective in reducing transfusion requirements and blood volume without increasing the risk of thromboembolic complications in primary total hip arthroplasty compared with IV or topical administration.

Tranexamic acid significantly reduces blood loss in a wide range of surgical procedures and improves survival rates in trauma patients with severe bleeding. Although it acts mainly as a fibrinolysis inhibitor, it also has an anti-inflammatory effect and may help to alleviate the systemic inflammatory response syndrome seen in some patients who have undergone cardiac surgery. However, high-dose tranexamic acid administration has been associated with seizures and other adverse effects that increase the cost of care, and tranexamic acid administration to reduce perioperative bleeding should be standardized. Tranexamic acid is well tolerated with most adverse reactions considered mild or moderate. Severe events are rare in clinical trials, and literature reviews have shown tranexamic acid to be safe in several different surgical procedures.

## 3.2. Purpouse and objectives

This paper investigates the dose-dependent efficacy of tranexamic acid in patients who underwent hip and knee arthroplasty, patients hospitalized in the Orthopedic and Traumatology Department of the County Emergency Hospital of Sibiu. Of these patients, twenty received a single dose of tranexamic acid preoperatively, while twenty received two doses of tranexamic acid.

The main objective of this work is to investigate whether a single preoperative dose, administered as a 500 mg/5ml vial thirty minutes preoperatively, has the same efficacy as administering two doses: one preoperatively, as a single dose, and one postoperatively, eight hours after surgery, each dose consisting of 500mg/5ml.

A second objective is the rate of deep vein thrombosis following arthroplasty and tranexamic acid administration.

The third objective is to highlight whether there is a difference in the risk of bleeding and whether there is a quantitative difference when two doses of tranexamic acid are given.

## 3.3. Matherials and methods

The present work is an observational, prospective study that included 40 patients who underwent hip and knee arthroplasty. The patients were selected in a randomized fashion, 40 patients who were consecutively operated in the Orthopedic and Traumatology Clinical Section of the County Emergency Hospital of Sibiu [129]. The first patient received one dose of tranexamic acid, the second received two doses of tranexamic acid, the third received one dose of tranexamic acid and so on until the last one received two doses of tranexamic acid.

Diagnostic criteria included for venous thrombosis: hypoechoic or no echo cavity, minimal or absent blood flow signal in thrombosis, and a Doppler pulse explaining either lack of blood flow or lack of change with respiration. All patients underwent thrombotic prophylaxis with Enoxaparin 6000 IU administered subcutaneously. Initiation of therapy began 1 day before surgery, continuing for 25 days postoperatively.

During the operation, two doses of Lidocaine 10 mg/ml, one dose of Adrenaline 1mg/ml were administered intra-articularly; no drainage was used after the operation. During the PTG operation tourniquet was used, patients were mobilized immediately postoperatively with weight-bearing exercises (using a walking frame) and a range of passive range of motion after consultation with the Rehabilitation-Medical Department. Wound dressing was performed on days 1, 3 and 14 after surgery. The wound was monitored to assess for superficial infection, hematoma or seroma, major ecchymosis, suppuration, and flictene.

Patients were monitored during three distinct phases:

Preoperative phase:

- hemoglobin values one day before the operation

Postoperative phase:

- hemoglobin collection day 1 post-operative to observe the hemoglobin value
- blood count on postoperative day five to observe the hemoglobin value
- on day 6, bilateral Doppler ultrasound of the lower limbs was performed to look for signs of venous thrombosis

After discharge:

- on day 28 post-operatively, seven days after completion of prophylactic antithrombotic antithrombotic treatment, the second bilateral lower extremity Doppler ultrasound was performed to look for signs of venous thrombosis

Inclusion criteria: patients hospitalized in the Orthopedics and Traumatology Department of the Orthopedics and Traumatology Clinic of the Sibiu County Emergency Hospital, who underwent hip and knee arthroplasty.

Exclusion criteria: patients with a history of DVT, patients with an infection, patients on anticoagulant therapy for cardiologic pathology, patients with preoperative hemoglobin less than 11 g/dL for women and less than 13 g/dL for men, patients with inadequate screening in the postoperative period. During follow-up, two patients in the two-dose group were lost to follow-up, as they did not show up for the 30-day postoperative follow-up.

## 3.4. Results

### 3.4.1. Distribution by hemoglobin value on admission

Hemoglobin values on admission were between 11 and 15 mg/dl.

Among the 38 patients included in the group: 13 patients have inpatient hemoglobin values between 11-13 mg/dl; 22 patients have inpatient hemoglobin values between 13-15 mg/dl; 2 patients have inpatient hemoglobin values higher than 15 mg/dl.

Of the patients: 58% had inpatient hemoglobin in the range of 13-15 mg/dl, less than 34% of the patients had inpatient hemoglobin in the range of 11-13 mg/dl, while 5% of the patients had inpatient hemoglobin greater than 15 mg/dl.

The minimum Hb on admission was 11 mg/dl, the maximum on admission was 16 mg/ dl and the mean value was 13.3421 mg/ dl.

### 3.4.2. Hemoglobin value according to the number of tranexamic acid doses administered

For patients given a single dose of tranexamic acid, the mean Hb on postoperative day 1 is 11.4250 mg/dl with a standard deviation of 1.28672.

For patients given two doses of tranexamic acid, the mean hemoglobin on day 1 is 11.5889 mg/dl with a standard deviation of 1.39364.

For patients who received a single dose of tranexamic acid, the mean hemoglobin on day 5 is 10.5600 mg/dl with a standard deviation of 1.32602.

For patients who received two doses of tranexamic acid, the mean hemoglobin on day 5 is 10.7333 mg/dl with a standard deviation of 1.51619.

For patients with a single dose of tranexamic acid administered, the mean Hb difference between preoperative day and day 1 is 1.8900.

For patients with two doses of tranexamic acid administered, the mean Hb difference between day 1 and day 5 is 1.8500.

For patients with a single dose of tranexamic acid administered, the mean Hb difference between day 1 and day 5 is .8700.

For patients with two doses of tranexamic acid administered, the mean Hb difference between day 1 and day 5 is .8556.

### 3.4.3. Distribution by number of tranexamic acid doses administered

Of the 38 patients, 18 patients received 2 doses and 20 patients received 1 dose. 47% of patients included in the study received 1 dose of tranexamic acid and 53% of patients received 2 doses of tranexamic acid.

### 3.4.9. Distribution by number of tranexamic acid doses administered and transfusion requirements

Of those with 1 dose of tranexamic acid administered, 3 patients received blood transfusion.

Of those with 2 doses of tranexamic acid administered, 2 patients received blood transfusion.

In both cohorts, a subset of patients required blood transfusions. In the single-dose tranexamic acid group, three patients received transfusions, two of whom were transfused immediately after surgery, while one patient required a transfusion after control hemoglobin measurement 5 days postoperatively. Similarly, in the two-dose tranexamic acid group, two patients required transfusions, both administered immediately postoperatively.

### Doppler ultrasound

Doppler ultrasound examinations revealed a single case of partial thrombosis of the femoral vein in a 66-year-old woman (1.28%). Interestingly, intravenous tranexamic acid administration was not associated with a high risk of venous thromboembolic events.

### Complications

There were no major wound complications; no patients required additional dressing or wound care for superficial infection, hematoma, or seroma. No significant differences between groups were observed.

## 3.5. Discussions

The results of our study show that the use of TXA does not significantly increase the incidence of symptomatic venous thrombosis. The use of TXA in total knee arthroplasty as a routine method to prevent anticoagulation does not lead to an increased incidence of postoperative symptomatic symptomatic VTE. In our group, the incidence of DVT is only 1.28%, compared with other studies in which it is higher, approximately 8.6% [130]. In another study comparing the incidence of DVT in patients given intra-articular TXA and those not given TXA, the DVT rate was 4.3%. This study showed, like our study, no difference in DVT incidence between the two groups [131].

The patient who was diagnosed with deep vein thrombosis was prescribed Rivaroxaban, initially at a dose of 15 mg twice daily for 7 days and subsequently at a dose of 20 mg once daily for 23 days. At 30 days postoperatively, at re-evaluation, there were no signs of venous thrombosis or venous thromboembolic events. Of note, this patient had the highest BMI of all patients and was part of the group receiving a single dose of tranexamic acid, of note, all patients on two doses of tranexamic acid remained thrombus-free.

BMI is recognized as an independent predictor for VT, but it is inconclusive whether TXA administration played a decisive role in the thrombotic event [132]. In addition, numerous studies have investigated the incidence of VT following orthopedic procedures. In a study by Bin Abd Razak et al. among 531 Asian patients undergoing unilateral total knee arthroplasty without postoperative anticoagulation, only 4 individuals (0.75%) had symptomatic VTE, including one case of symptomatic pulmonary embolism [133]. In contrast, a meta-analysis by Januel et al, which included 44,844 cases of total hip arthroplasty or total knee arthroplasty with anticoagulation, reported overall rates of symptomatic VTE, deep vein thrombosis and pulmonary embolism after total knee arthroplasty of 1.09%, 0.63% and 0.27%, respectively [134].

In a retrospective study by Poeran et al, which covered 870 000 patients undergoing hip or knee replacement over six years in 510 US hospitals, deep vein thrombosis occurred in 0.4% of patients who received TXA and slightly more, 0.5%, in those who did not receive TXA [135]. In addition, a substantial body of literature indicates that TXA has a satisfactory safety profile, with no observed increase in VTE risk. These findings are similar to our result [109], [136], [137], [138], [139], [140].

Comparative analysis of hemoglobin levels on the first postoperative day showed a relatively uniform decrease in both study groups. A marginal difference of approximately 0.04 g/dL was observed, indicating a slightly greater mean decrease in hemoglobin among patients in the two-dose tranexamic acid group compared with the single-dose group. The mean decrease after the first PO day was 1.89 g/dL for patients who received one dose and 1.85 g/dL for patients with two doses. These changes in Hb level are comparable with other studies found in the literature [141].

This consistency in hemoglobin reduction persisted at postoperative evaluation on day 5 PO, with patients with a single dose of tranexamic acid showing a slightly greater mean decrease of approximately 0.015 g/dL. The mean decrease after day 5 PO was 0.87 g/dL for patients who received 1 dose and 0.855 g/dL for patients who received 2 doses. The double-dose group showed a comparable decline, reinforcing the consistent drug response in both groups. These results are different from those found in other studies that followed Hb for five days [142].

Our study found that there was no observed difference between the two groups in terms of Hb decrease on day 1 PO and also on day 5 PO, similar to some studies in the literature. Andrew G Golz's study performed on a group of about 1500 patients divided into two groups, as in our study, showed that there was no difference between the one-dose and the two-dose group, unlike other studies in the literature where there was a difference [143]. The study by Xiang-Dong Wu in a group of about 360 patients shows that with multiple doses, the decrease in Hb is less [142].

Another finding of this study is that there is no difference in blood transfusion requirements. Both groups demonstrated a similar pattern with two patients each requiring immediate postoperative transfusions again. The only difference was from a demo-graphic point of view; in the two-dose group there were two females who required blood transfusion, while in the one-dose group, two males required blood transfusion. At the five-day postoperative interval, only one patient required a transfusion, in the single-dose tranexamic acid group. This patient also had the largest decrease in Hb value between day one and day five, by 2.8 points. Blood transfusion requirements were very low, with only 13% of patients needing blood transfusion, confirming data from the literature [144]. Our study shows that there are no significant differences between these two groups, compared with other

studies that compared a two-dose, one dose administered intravenously and one intra-articularly [145].

In a meta-analysis by Reale et al. conducted in Pub Med, Web of Science, and Cochrane Library databases during January 2020 on complications of tranexamic acid use, 140 articles documenting 9067 patients who received tranexamic acid were identified. In particular, 82 studies focused on knee arthroplasty, 41 on hip arthroplasty, and 17 on other surgeries such as anterior cruciate ligament reconstruction, intertrochanteric fractures, and meniscectomies. Tranexamic acid intravenous protocol was studied in 111 articles, intra-articular in 45 and oral in 7. There were no differences in thromboembolic complications between the group receiving tranexamic acid and the control group, neither in the overall population ( 2.4% and 2.8%) nor in any other group based on the surgical procedure and route of tranexamic acid administration. They concluded that overall TXA did not increase the risk of venous thromboembolic complications regardless of the route of administration, supporting the safe use of tranexamic acid in patients undergoing surgery in the orthopedic sphere [146].

Yong -Ze - Yang et al. conducted a meta-analysis combining data from 5 studies that compared the efficacy and safety of a fixed dose of 1 g of tranexamic acid given intravenously with two 1 g doses given intravenously for hip or knee arthroplasty. This meta-analysis included randomized controlled trials and cohort studies comparing the efficacy and safety of different doses of tranexamic acid for hip and knee arthroplasty. Five cohort studies involving 5542 patients met the inclusion criteria. This meta-analysis showed that 1 dose of 1 g and 2 doses of 1 g iv tranexamic acid have equal efficacy in reducing blood loss, blood transfusion rate, postoperative hemoglobin level, and postoperative hospital stay after hip and knee arthroplasty without increasing the risk of postoperative complications. In patients at high risk of thromboembolic complications, a single dose of tranexamic acid of 1 g throughout surgery may be preferred [147].

We found no significant difference in wound complications such as superficial infections, hematoma or seroma between the two groups. These findings are comparable with data from other studies that have performed wound PO follow-up in patients who received TXA [148].

Strengths of the study are that it was a prospective study in a randomized selected group of patients. Subclinical DVT was also investigated, not only in symptomatic patients. Follow-up was performed until day 30 PO, several days after cessation of anticoagulant protection.

The limitation of the study was that we had a small number of patients.

## 3.6. Conclusions

Notably, the study addresses possible complications, particularly those related to the incidence of deep vein thrombosis (DVT). The findings indicate that there is no increased risk of DVT in the group of patients who received two doses of tranexamic acid. The absence of an increased risk of deep vein thrombosis (DVT) among those who received a second dose further supports the hypothesis that the additional dose may not be necessary [129].

In conclusion, this compelling evidence presented suggests that the administration of a second dose of tranexamic acid may not be necessary as indicated by analysis of hemoglobin levels and transfusion requirements [129].

A first argument is that no advantage was observed for hemoglobin values if a second dose of tranexamic acid was given. Thus, comparable reductions in hemoglobin were observed in patients who received a single dose and those who received two doses. This emphasizes that an additional dose does not result in a more substantial decrease in hemoglobin nor does it confer any advantage in terms of postoperative management of blood transfusion [129].

Furthermore, the analysis of blood transfusion requirements validates the idea that a second dose of tranexamic acid may not be justified. The data evoke no discernible trend of reduced transfusion requirements among patients who received a second dose compared to those who received a single dose. This nuances the fact that the additional dose does not provide any tangible benefit in terms of mitigating the likelihood of postoperative transfusions [129].

# GENERAL CONCLUSIONS

Total hip and total knee replacement surgery are commonly used therapeutic solutions to relieve pain and improve functionality in patients with degenerative joint conditions. However, these procedures are not without risks, and postoperative complications can have a significant impact on patients' clinical outcomes and quality of life. Ranging from periprosthetic infections and deep vein thrombosis to dislocations and prosthetic damage, the management of these complications is essential for the long-term success of surgery.

The study highlights the importance of monitoring inflammatory proteins, such as C-reactive protein (CRP), eritrocite sedimentation rate (ESR) and fibrinogen, in the early diagnosis of periprotic infections. These assessments not only facilitate early identification of possible complications, but are also essential for monitoring the effectiveness of treatment in affected patients. Studies have shown that these inflammatory markers showed a significant increase in the first 12-24 hours after surgery, peaking on days 5, 7 and 21. Normalization of these markers occurs gradually, usually within a few weeks, which underlines the need for careful and continuous monitoring in the postoperative period.

In this work, significant but minimal differences in the variation and normalization trend of the analyzed parameters between the two groups of patients were identified. However, a slower trend of normalization of values was observed in patients who underwent total knee arthroplasty compared to those who underwent total hip arthroplasty. This finding suggests that knee surgery may require a longer time to reach normal parameters.

The study results demonstrated that C-reactive protein (CRP) is a sensitive and specific marker in the early diagnosis of postoperative infections, manifesting as significant increases in affected patients. This observation underlines the crucial importance of monitoring CRP levels in the perioperative period, as early detection of changes may facilitate rapid and effective interventions, thus contributing to improved clinical outcomes and reduced postoperative complications.

The results obtained in this study are aligned with those presented in the literature, reinforcing the concept that the use of inflammatory and hematologic markers can have a significant impact on the management of patients who have undergone total arthroplasty. This approach allows a more accurate assessment of the clinical status of patients and facilitates informed decisions in postoperative treatment, thus contributing to the optimization of the recovery process and reducing the risks associated with surgery.

Rigorous monitoring of perioperative biological parameters, in particular C-reactive protein (CRP), plays a key role in the early identification and effective management of infections. This approach not only improves clinical outcomes, but also contributes to reducing morbidity associated with total hip and knee arthroplasty procedures. By implementing appropriate monitoring protocols, rapid interventions can be facilitated to minimize postoperative complications and optimize patient recovery.

C-reactive protein remains a basic biomarker for the assessment of infectious complications and plays an important role in the detection of inflammatory processes. However, for the proper diagnosis

and management of periprotic infections, other tests for higher specificity should be used to provide greater accuracy in identifying the type and severity of infection. This integrated approach can contribute significantly to improving therapeutic interventions and preventing long-term complications.

The results of the study show significant differences in postoperative CRP values in patients with joint infection, with higher than normal levels of this inflammatory marker in those who had an infection after total hip replacement (THR) compared to those who had total knee replacement (TKR), with lower values in those with infection compared to the normal favor. These differences suggest that the type of prosthetized joint may influence the postoperative inflammatory response in the context of infection.

Pre-operative screening plays an essential role in the rigorous preparation of patients for S and GTP. By sampling for urinary tract infections, pharyngeal exudate and inguinal folds, surgeons can assess both the patient's general health and possible sources of infection that could compromise the success of the procedure. This preventive screening approach helps to reduce the risk of postoperative infections and ensures that patients are in the best possible state to cope with the surgical procedure. The observations of this study are consistent with findings in the literature, which support the importance of preoperative screening in preventing complications.

Identification of asymptomatic infections before surgery has a significant relationship with the incidence of periprotic infections. In the group of patients who underwent hip arthroplasty after femoral neck fracture, 85% of those who subsequently developed a periprosthetic infection had an asymptomatic infection before surgery. However, in 50% of cases, the pathogens identified preoperatively were identical to those implicated in periprosthetic infections, suggesting variability in infectious sources and the importance of continuous monitoring.

In terms of pathogens identified, the results of this study show that Escherichia coli bacteria are almost exclusively present, accounting for 87.5% of infections. The remaining percentage is attributed to Staphylococcus, which was identified in 12.5% of cases. These results emphasize that in patients presenting with asymptomatic infections at the time of presentation for surgery there is a very high likelihood that Escherichia coli is the predominant pathogen involved in periprotic infections.

Statistical data obtained in terms of treatment response of preoperative asymptomatic infections indicate encouraging results for the effective management of these infections. Uroculture, being the main source of positive results in the preoperative phase and exclusively detecting Escherichia coli bacteria, showed a maximal response to the treatment administered, demonstrating a high sensitivity of this pathogen to the applied therapies. In parallel, the nasal exudate also showed a 100% success rate in eradicating the infections identified, even though the pathogens detected were more varied, including both Escherichia coli and Staphylococcus in approximately equal proportions. A particularly important aspect, which underlines the effectiveness of current therapeutic approaches, is that this maximum percentage of response to treatment is maintained even in infections caused by multi-drug resistant bacteria. This suggests that the treatments applied have been sufficiently potent and specific to combat even those infections that might be more difficult to treat under other clinical conditions. Thus, the results underline the importance of preoperative screening and targeted treatment, which can help to prevent periprotic infections and optimize patients' health before surgery.

The current study supports the results presented by other research in the literature, confirming the significant benefits of diagnosis and treatment of preoperative asymptomatic infections. These findings emphasize the importance of proactively addressing asymptomatic infections, which not only helps to reduce the risk of postoperative complications, but also to improve the overall health status of patients before surgery. Thus, preoperative screening and treatment proves to be an essential part of a well-founded and effective surgical preparation plan.

A noteworthy aspect of the study is the treatment of possible complications, particularly those related to the incidence of deep vein thrombosis (DVT). The findings suggest that there is no increased risk of DVT among patients who were treated with two doses of tranexamic acid. These results suggest a reassessment of preoperative treatment protocols, as the risks associated with additional drug administration may not be justified in the context of clinical benefit.

The compelling evidence presented in this study suggests that a second dose of tranexamic acid may not be necessary. This conclusion is supported by the analysis of hemoglobin levels and transfusion requirements, which indicate that the clinical results obtained do not justify an additional dose. Thus, a reconsideration of the therapeutic protocol is warranted in view of the proven efficacy of the initial doses and the positive impact on the management of risks associated with blood transfusion.

A first argument in support of this conclusion is that, in terms of hemoglobin values, no significant benefit associated with the second dose of tranexamic acid was observed. In analyzing the data, it was found that patients who received a single dose showed comparable reductions in hemoglobin to those who received two doses. This result suggests that an additional dose of tranexamic acid does not contribute to a more pronounced decrease in hemoglobin levels and therefore does not provide benefit in terms of blood transfusion management in the postoperative period. Thus, a clarification of the role of tranexamic acid is emerging, highlighting the efficacy of single-dose administration in preventing blood loss without the need for additional interventions.

Analysis of blood transfusion requirements further supports the idea that a second dose of tranexamic acid may not be justified. The data from the study do not show a clear trend towards a reduction in transfusion requirements among patients who received this additional dose compared to those who were treated with a single dose. This suggests that administering an additional dose does not offer significant benefit in terms of reducing postoperative transfusion risks, thus emphasizing the need to reconsider treatment strategies in this context.

The results obtained in this study are in full agreement with those presented in the literature, reinforcing the concept that the use of inflammatory markers and hematologic parameters has a significant impact on the management of patients who have undergone total arthroplasty. This is because these markers can provide valuable information about the patient's health status, helping to identify possible complications early and to monitor response to treatment. By integrating these data into the decision-making process, physicians can develop personalized treatment strategies that meet the specific needs of each patient.

This approach not only facilitates informed decision-making in postoperative treatment, but also contributes to optimizing the recovery process by reducing hospitalization time and the risks associated with surgery. In addition, careful management of inflammatory markers can improve long-

term outcomes, thereby supporting patients to achieve optimal joint function and a higher quality of life. Therefore, the integration of these markers into clinical assessment is not only beneficial, but becomes an essential component in the postoperative care of patients.

## Personal contributions and original elements of the thesis

C-reactive protein is a fundamental biological element in the biological evaluation of infectious complications; at the moment, it still needs to be complemented with other tests with higher specificity for the diagnosis and further treatment of periprotic infections. The performed study could be a first step to further investigate these postoperative CRP values in patients with joint infection. We observed that CRP has higher values for a longer time in infections after PTȘ and contrary to expectations in PTG it shows lower values. This study could provide a starting point for further investigation of postoperative CRP values in patients with joint infection.

Analysis of asymptomatic infections demonstrates the benefit of treating these infections preoperatively to reduce the risk of postoperative infectious complications. In the group of patients with hip arthroplasty after femoral neck fracture, 85% of those who developed a periprosthetic infection also had an asymptomatic infection preoperatively. The pathogens identified preoperatively were identical to those responsible for periprosthetic infections in 50% of cases.

The study demonstrates that we do not have a higher incidence of deep vein thrombosis and pulmonary embolism after tranexamic acid in patients undergoing total hip and knee arthroplasty, regardless of the dose administered. We also found that we had no significant difference in the postoperative hemoglobin decrease, regardless of the dose of tranexamic acid administered to the patients.

## The limits of own research

First, one of the important limitations of the present study is the relatively small number of patients enrolled in the studies.

Another rather important limitation in this research is the lack of sufficient follow-up of postoperative patients.

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# List of abbreviations

DVT - Deep vein thrombosis

PE - Pulmonary embolism

ACL - Anterior Cruciate Ligament

PCL - Posterior Cruciate Ligament

THR - Total hip replacement

TKR - total knee prosthesis

VTE - venous thromboembolism

DOAC - direct anticoagulants

LMWH - low molecular weight heparins

UFH - unfractionated heparins

HHSV - heme sedimentation rate

CRP - C-reactive protein

MSSA - Methicillin Susceptible Staphylococcus Aureus

MRSA - Methicillin-resistant Staphylococcus aureus

Hb - Hemoglobin

CM Rod - Center-medullary rod

TXA - tranexamic acid

IV - intravenous

BMI - body mass index

# List of publications

Bocea, B.-A.; Roman, M.-D.; Ion, N.C.I.; Fleaca, S.R.; Mohor, C.-I.; Popa, D.A.; Mihaila, R.-G. Diagnostic Values of Serum Inflammatory Biomarkers after Hip and Knee Arthroplasty in Patients with Periprosthetic Joint Infection. Healthcare 2024, 12, 1511. https://doi.org/10.3390/healthcare12151511

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