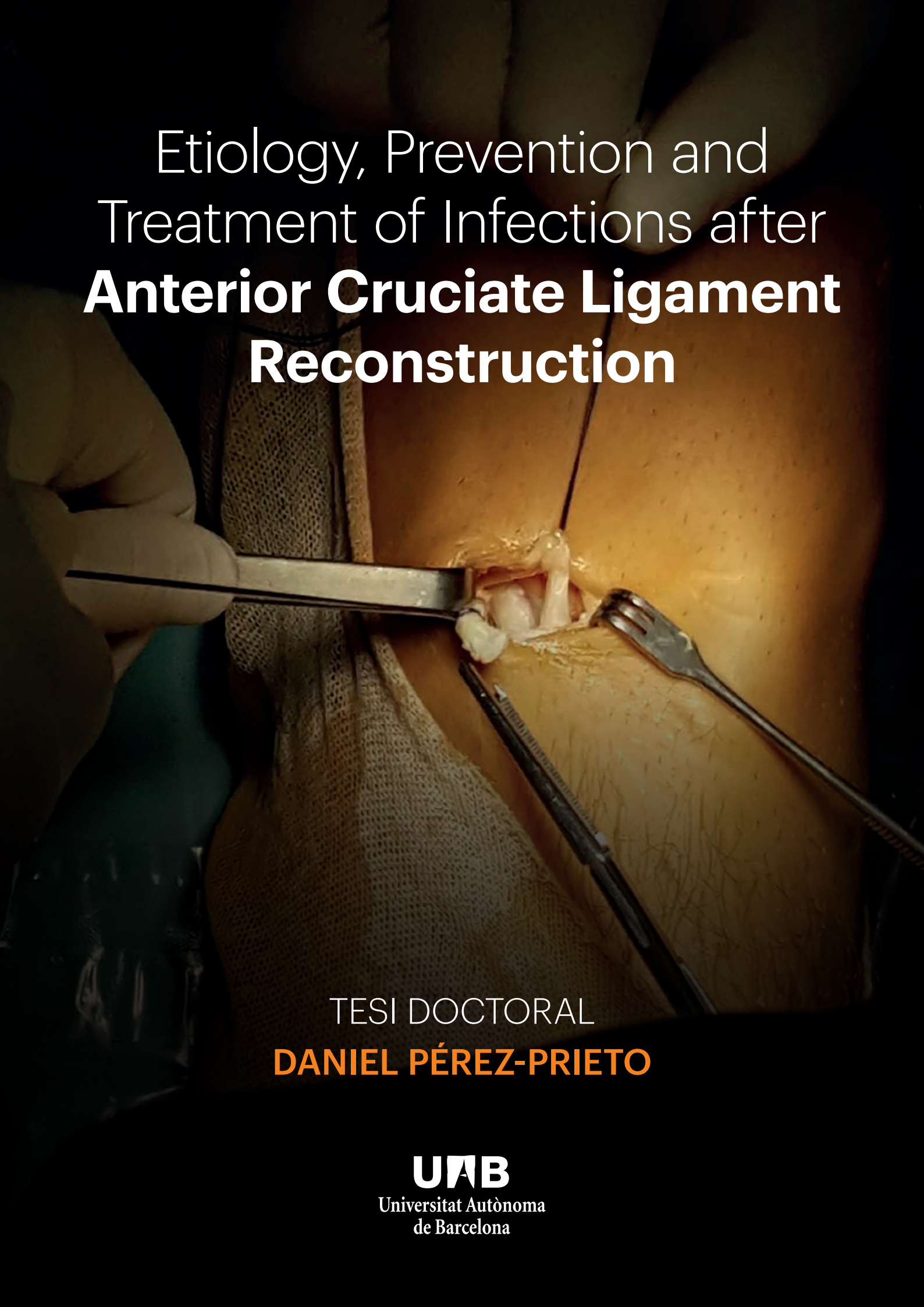
Universitat Autònoma de Barcelona

Etiology, Prevention and Treatment of Infections after Anterior Cruciate Ligament Reconstruction

Daniel Pérez-Prieto



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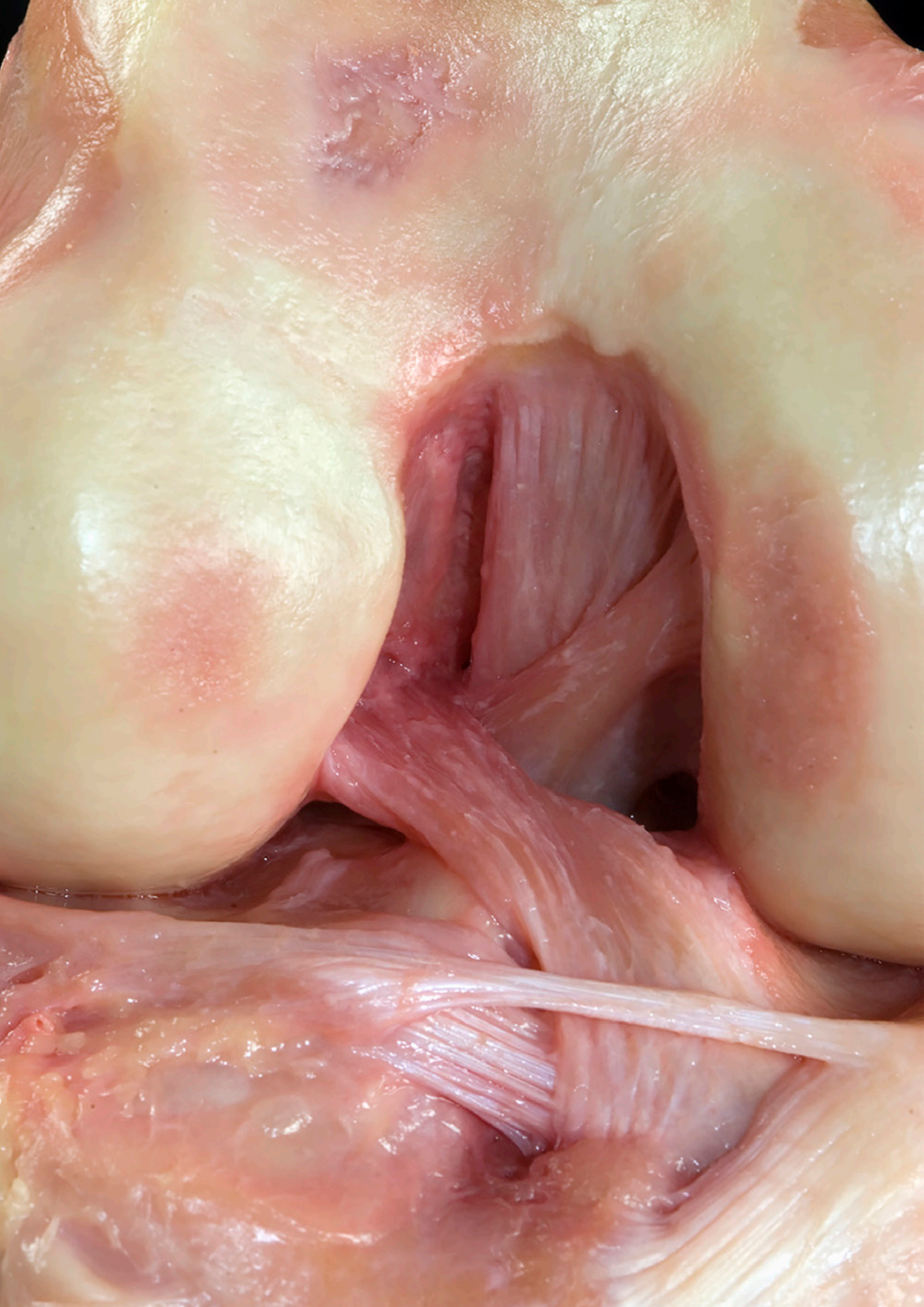

Etiology, Prevention and Treatment of Infections after **Anterior Cruciate Ligament Reconstruction**

TESI DOCTORAL

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CERTIFIQUEN:

Que el treball d'investigació titulat:
"ETIOLOGY, PREVENTION AND TREATMENT OF INFECTIONS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION",

ha estat realitzat sota la nostra direcció i està en condicions per presentar la seva lectura i defensa davant el tribunal corresponent per obtenir el grau de Doctor.

I per tal que consti als efectes oportuns, signem el present document a Barcelona, maig de 2018

Prof. Dr. Joan Carles Monllau

Dr. Lluís Puig

Dr. Andrej Trampuz

La tesi doctoral amb títol **Etiology, Prevention and Treatment of Infections after Anterior Cruciate Ligament Reconstruction** i presentada pel doctorand Daniel Pérez-Prieto, ha estat realitzada sota compendi de publicacions seguint la normativa de la Universitat Autònoma de Barcelona per aquest tipus de tesi doctoral.

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Pérez-Prieto D, *Portillo ME, Torres-Claramunt R, Pelfort X, Hinarejos P, Monllau JC. Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated. Knee Surg Sports Traumatol Arthrosc. 2018 Feb;26(2):558-562*

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Agraïments

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A Xavi, Gemma i Olívia. Pel vostre suport durant aquests anys.

“Non est ad astra mollis e terris via”

Séneca

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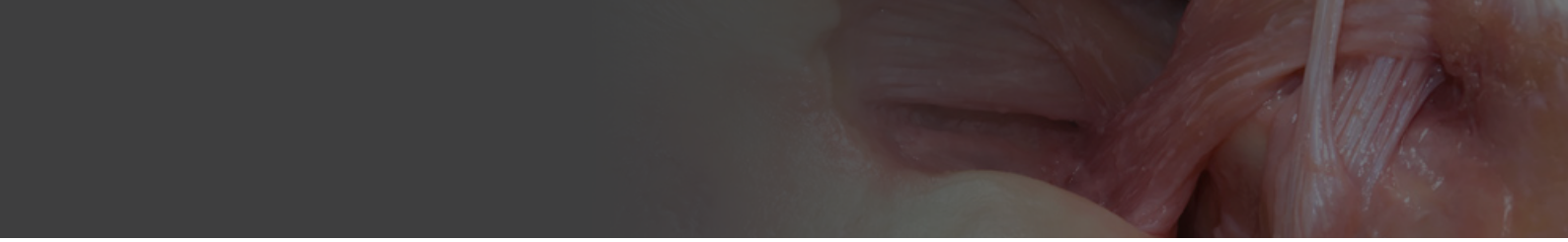

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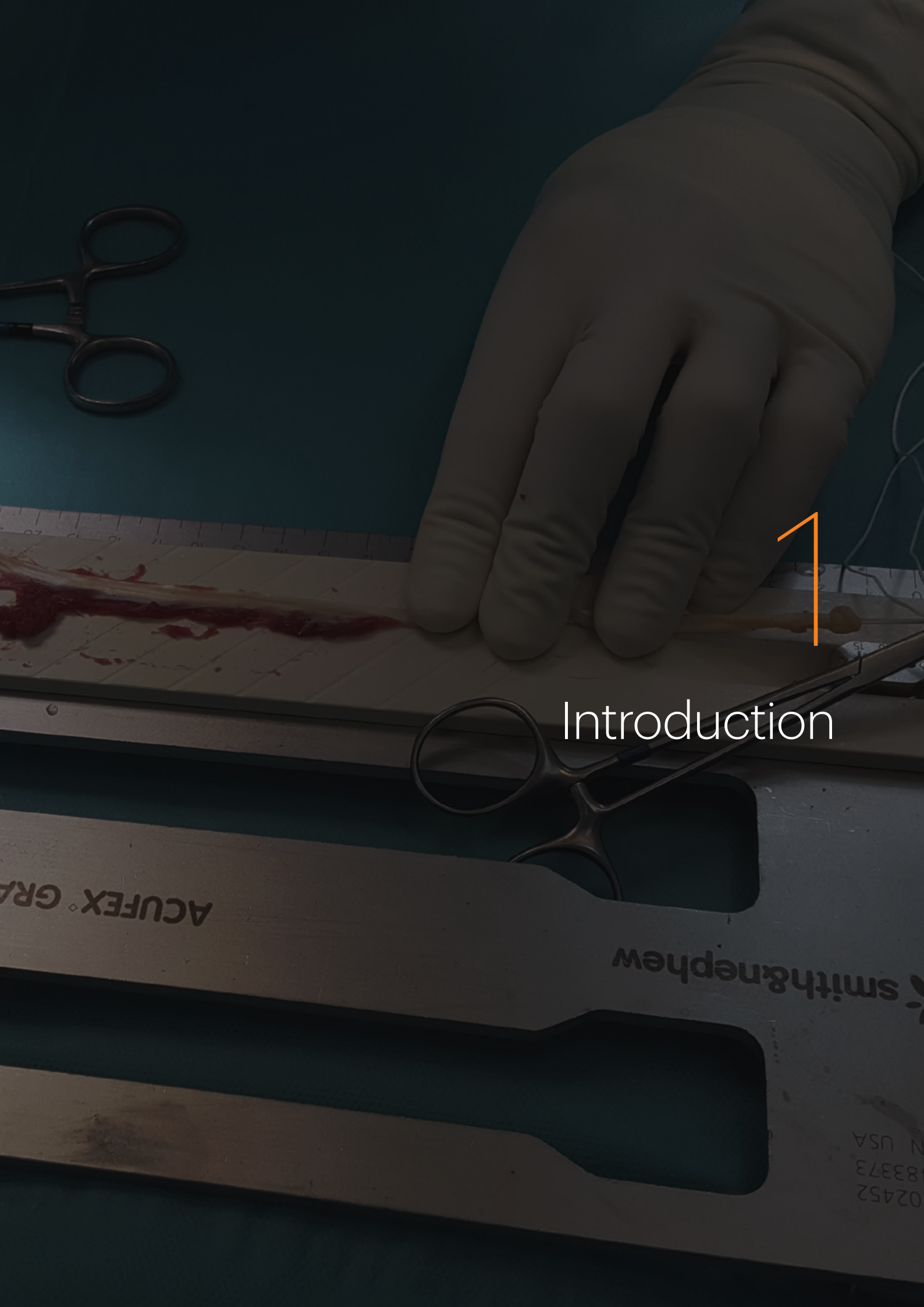


1 Introduction

Introduction

The anterior cruciate ligament (ACL), located inside the knee joint, acts as the anterior restraint between the tibia and the femur during movement. It also has an important function in rotational knee control[1]. This is the classical biomechanical role that is obviously due to the direction of its collagen fibres. From its origin in the external wall of the intercondylar notch, those fibres run oblique to the anterior tibial spine. Moreover, studies of the ACL have determined that it plays an important role in making for adequate proprioception. Therefore, ACL injuries are disabling, especially in terms of sports activities[2]. Thus, the need for ACL surgery has significantly increased over the last 20 years and the number of studies of the ACL have more than doubled over the last 10 years[3].

1.1 Anterior Cruciate Ligament injury

1.1.1 Prevalence of Anterior Cruciate Ligament Reconstruction injury

ACL reconstruction has come to be the most frequently performed surgery for ligament injuries. In the United States, some 200,000 anterior cruciate ligament reconstructions (ACL-R) are done per year[4]. In Spain they come out at some 17,000 surgeries per year[5].

In part, an increase in the practice of recreational sports has raised the number of non-professional athletes diagnosed with this injury. Other factors that explain that increase are the increasing knowledge of ACL anatomy, the development of the associated surgical techniques as well as studies of sequelae in non-treated cases[6].

1.1.2 Mechanism of Injury

Most injuries occur due to an indirect mechanism in a sportive context (72%) while the rest are caused by direct trauma[7]. An extended or hyper-extended knee followed by a sudden valgus-external rotation movement is the most widely seen cause of injury[8,9].

Sports that present the highest risk of ACL injury are those in which the femur frequently pivots over the tibia. They include football, rugby, basketball, tennis, ski, etc.[8,9]

1.1.3 Diagnosis of ACL injury

Physical examination is crucial to properly diagnosing ACL injuries[10]. Lachmann and anterior drawer tests are static examinations in which a force is applied from posterior to anterior at 30º and 90º respectively. The pivot shift test is a dynamic examination to assess the rotational stability of the knee. To perform it, a stress force in valgus with the knee fully extended with internal rotation is applied. Then, maintaining these forces, knee flexion is started and the tibial plateau moves anteriorly, reproducing a clicking sound.

When a clinical suspicion exists, the study should be completed with Magnetic resonance imaging (MRI) to confirm it. It has a 97% reliability rating in complete ACL tears[11]. Even though an MRI can help in LCA injury diagnoses and it is crucial to ruling out other concomitant injuries, it is important to keep in mind that the key to diagnosing LCA tears is a clear injury mechanism along with a physical examination.

1.1.4 Anterior Cruciate Ligament reconstruction

There are thousands of studies of ACL surgery and the reconstruction technique has been improving year-on-year. The most important advance has been in using anatomic reconstruction of the ligament with the aid of an accessory anteromedial portal or a Gillquist portal instead of using transtibial techniques[12]. The anatomic femoral tunnel provides better rotational stability than non-anatomic techniques[13,14]. To find the anatomic footprint in the femoral condyle, it is important to hyperflex the knee and create a tunnel which is lower than the one done previously.

The tibial tunnel procedure has not changed as it has always used the anatomic footprint of the native ACL. The tibial tunnel is made between 1-2 cm medially to the anterior tibial tubercle with an angulation of 55º on the sagittal plane and 20º on the coronal plane.

Once the tunnels are made and the graft has been put in place, it can be fixed with several techniques like bioresorbable interference screws, staples and cortical suspensory fixation in the case of hamstring grafts.

1.1.5 Graft choice in ACL reconstruction

There are different graft alternatives when ACL reconstruction surgery is to be performed. When the choice is an autologous tendon, it can be the patellar tendon, hamstrings or quadricipital tendon.

The patellar tendon (bone-patellar tendon-bone, BPTB) is one of the most widely used. It has a bone block from the distal part of the patella and another one from the anterior tibial tubercle. Some of its advantages are that it can be easily integrated and, as some studies suggest, it may be less prone to infection[15,16].

The other autologous graft that is also widely used is the hamstring graft (gracilis and semitendinosus). This choice has no bone block and therefore integration in bone tunnels may be more difficult[17]. However, studies have shown similar functional results to BPTB. As previously stated, there are some studies that suggest that this graft may be related to a superior incidence of postoperative infections. Some authors have linked this risk to the somewhat trickier graft harvesting and preparation process[18].

Finally, the choice of allografts has seen a rise in recent years in the USA as it does not produce donor site morbidity like pain, loss of muscle power, scarring, etc. However, it has also several disadvantages like the cost, bone integration issues as well as the remote possibility of disease transmission. Therefore, it is reserved for revision cases in Europe[19].

1.2 Infection after Anterior Cruciate Ligament reconstruction

1.2.1 Orthopedic related infections

Implant related infections have become an important field of study in orthopedics. Since the identification of biofilm, significant work has been done to eradicate it.

Gristina and Costerton were the first authors to describe the role of biofilm in orthopedic devices[20]. They explained how the bacteria attach to the foreign body and then produces the layer or glicocalix to protect themselves against antibiotics or leucocytes[21]. That is how bacteria can survive in dormancy for years without interacting with the surrounding tissues.

Some authors found that the number of bacteria needed to infect a wound was between 1,000 and 10,000 times lower when stitches were put in subcutaneously than when there is no material in place[22,23]. This because the sutures act as a foreign body on which bacteria can attach themselves and form a biofilm.

Soon after those findings came to light, orthopedic surgeons realized that there was no way to cure orthopedic infections except by removing the implant. Then, the two-stage exchange became popular[24,25]. It was a time when no antibiofilm antibiotics were in use. Then, the only way to treat it was to completely kill the bacteria by removing the prosthesis[26].

In the late 90's Zimmerli carried out the very first clinical trial on prosthetic joint infections (PJI) with antibiotic treatment[27]. In it, he proved that rifampicin has an antibiofilm activity that can kill not only planktonic bacteria but also the dormant biofilm bacteria. This finding opened a new treatment era in which removal of the prosthesis was not mandatory to cure PJI as a powerful antibiofilm antibiotic can be combined with surgery.

Since then, some other advances have been published on the treatment of PJI, and, as of

lately, in other implant related infections, such as osteosynthesis devices, spinal fusion surgery as well as arthroscopic surgery.

1.2.2 Etiology and epidemiology of ACL-R infections

The literature on ACL-R infections is less extensive than that on PJI. Most of the studies are descriptive studies and some clinical trials on surgical treatment have recently been published.

Infections after ACL-R are a frequent complication with a top reporting rate of 1.8%[18]. It is less frequent than PJI, which can be explained by the less aggressive approach and therefore less harm to soft tissues. Another explanation may be the smaller number of foreign bodies that the bacteria can attach to and thereby favor biofilm formation.

The vast majority of ACL-R infections are acute infections and up to 90% are caused by staphylococcal species[16,16,28,29]. One interesting fact is that differently to PJI in which acute infections are commonly caused by Staphylococcus aureus, coagulase negative staphylococci (CNS) are frequently isolated in acute ACL-R infections. One theory is that these microorganisms may come from the harvesting and preparation process[30]. Other isolated bacteria are cutibacterium acnes, enterococcus species and Gram negative bacilli (GNB).

1.2.3 Treatment approach to ACL-R infections

Like other implant related infections, the key to curing an infection after ACL-R is to combine surgical debridement and antibiotic treatment. There is good evidence that an optimum combination of both treatments can achieve a cure rate of close to 100%[18,31]. In fact, there are only a few case reports describing chronic osteomyelitis due to ACL-R infection[32,33].

There is an important difference between PJI and infections after ACL-R as PJI always needs open debridement and the ACL can be successfully debrided arthroscopically. There is also evidence that several arthroscopic debridement procedures can be performed without compromising infection curing[31,34]. To do so, a well fixed and viable graft must be confirmed intraoperatively and a Stage IV Gächter synovial reaction has to be excluded[35].

Antibiotic treatment has not been well evaluated in ACL-R infections. All studies confirm that it should be combined with surgery, but none of them give information about the antibiotics that were used. Therefore, some authors have extrapolated the concept of biofilm treatment of PJI to the ACL[30].

1.2.4 Outcomes after ACL-R infections

Once the infection is cured, the main concern is whether it can affect functional outcomes. Historically, there was a belief that infections could compromise range of motion as arthrofibrosis may arise. Pain was also supposed to jeopardize returning to sports activities. However, most of studies and reviews seem to suggest that when an ACL-R infection is correctly treated and the infection is cured, functional outcomes and a return to sports are similar in non-infected cases[28,36]. Other studies that obtain worse outcomes in the infected group may be biased because they compare professional and amateur athletes and their outcome expectations are not comparable[18].

1.3 Studies basis

The first study included for this thesis proposal *(Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated)* aimed to seek validation for a new ACL infection prevention protocol. For that purpose, it is important to take the results of Vertullo et al. into account for the same technique[37]. They used a 5mg/dl vancomycin solution to pre-soak ACL hamstrings autografts. By doing so, the infection rate was reduced to 0%. However, this was the only study of this technique and the authors only studied hamstrings autografts. Therefore, in this first study, our aim was to see whether the results of the vancomycin soaking technique were consistent with those obtained by Vertullo et al. Additionally, the question as to whether it could act similarly regardless of the graft choice was posed.

Introduction

Given the results obtained in the first study, the authors of the second study *(Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated)* aimed to explain the results of the first study. In that sense, following the results obtained by Badran et al[38], it was postulated that contamination can occur during ACL graft harvesting and preparation. Then, the effect of the vancomycin soaking technique on the contamination was studied in the second study as way to explain infection reduction by using this technique.

In the third study *(Infections after Anterior Cruciate Ligament Reconstruction: Which Antibiotic after Arthroscopic Debridement?)*, the kind of treatment that should be performed in those cases in which infection cannot be prevented was analyzed. Since no studies on ACL infection antibiotic treatment have been reported, an extrapolation of biofilm studies on prosthetic joint infection (PJI) was made[39].

Finally, a review of the literature on ACL-R infections *(Managing septic arthritis after knee ligament reconstruction)* has been added as a complementary study for this thesis.

Those three clinical studies published in high impact orthopedic journals were made in the field of ACL-R infections. The review added has been also published in a high impact factor orthopedic journal.

Here, infections after ACL-R are studied from three different angles. First, the prevention of infection and the use of a technique to reduce the infection rate is studied. Second, the source of contamination and the way to reduce it using the that technique is looked at. Then, we move on to the management of infection, dealing with which antibiotic schedule should be used among other aspects. Thus, the prevention, etiology and treatment of the ACL-R infection are at the core of this thesis.

1.4 Hypothesis

1.4.1 Hypothesis 1st study

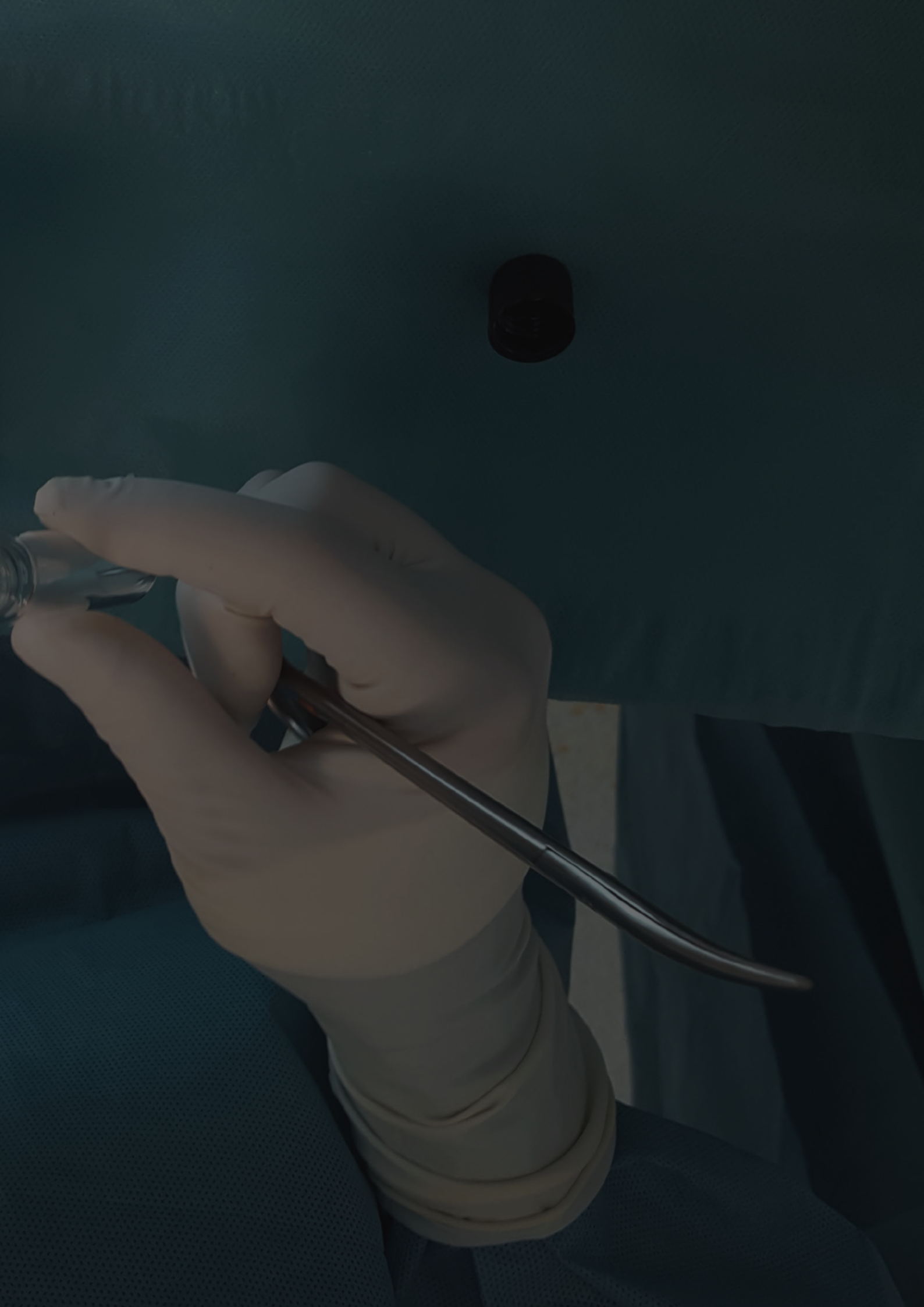
Prophylactic autograft presoaking in vancomycin along with a prophylactic intravenous (IV) antibiotic reduce the incidence of infection after ACL-R.

1.4.2 Hypothesis 2nd study

The vancomycin solution reduces contamination rates during ACL graft harvesting and preparation.

1.4.3 Hypothesis 3rd study

The combination of levofloxacin and rifampicin is an effective treatment for ACL-R staphylococcal infections.



2

Material and Methods

Material and Methods

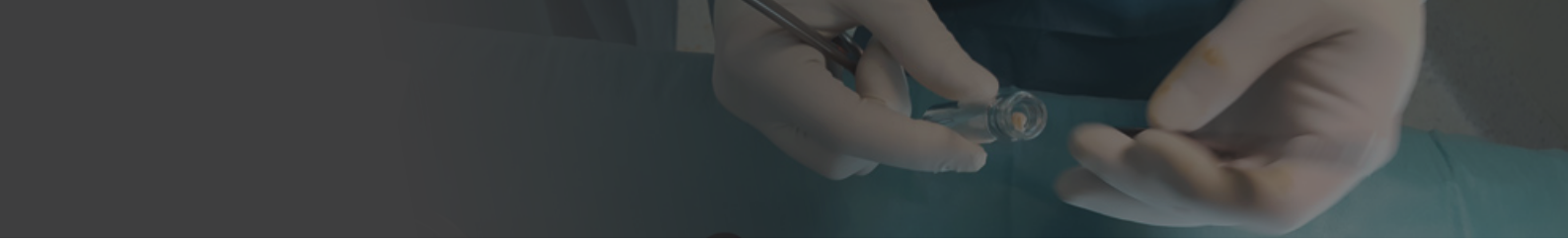
2.1 First study

Autograft soaking in vancomycin reduces the risk of infection after anterior cruciate ligament reconstruction.

In the first study, a retrospective review of all the patients that consecutively underwent primary arthroscopic ACL-R with an autograft in two University Hospitals was performed. Those patients who needed an extra-articular procedure or those who received an allograft were not included in the study. In the initial 4-year period, the patients received preoperative IV antibiotics (group 1). In the following 4-year period, the patients received preoperative IV antibiotics and, furthermore, the graft was presoaked in a vancomycin solution (group 2).

2.1.1 Surgical technique

All patients were operated on by the same surgical team composed of four senior surgeons. All operations were performed on an outpatient basis. The prophylactic antibiotic protocol consisted in a single dose of 2 g of preoperative IV cefazolin or a single dose of 1 g of preoperative IV vancomycin if a penicillin allergy was reported. No patient in this series informed of a vancomycin allergy. The types of grafts employed were quadrupled hamstrings and a BPTB. A pre-tension of 80N was applied for 5 minutes before fixation of the hamstrings grafts. BPTB grafts were fixed using a resorbable interference screw in both sides. The hamstring grafts femoral fixation was carried out with either a transversal fixation (Cross-Pin system®, Stryker, Kalamazoo, MI, USA) or with a cortical suspensory fixation system (XO Button Fixation System®, ConMed Linvatec, Largo, FL, USA). Tibial fixation was accomplished with a resorbable interference screw. No drains were left after surgery. The technique of vancomycin saturation was performed as previously described by Grayson et al[37]. A solution of 100 ml of sterile saline was placed in a tray and mixed with 500 mg of vancomycin powder. When the graft had been obtained and prepared, it was immersed in the tray and then wrapped in gauze that had been saturated with this vancomycin solution beforehand. The graft was left there for 10–15 min (until it was used for the ACL reconstruction).



2.1.2 Diagnostic criteria for septic arthritis

The diagnosis of septic arthritis was based on the patients' anamnesis and physical examination, laboratory parameters and cultures of synovial fluid and/or joint tissue. Synovial aspiration was performed as soon as the diagnosis was suspected. The liquid obtained was immediately sent for biochemical analysis and cell count analysis in heparin tubes. The remaining synovial fluid was introduced into aerobic and anaerobic blood culture bottles for automatic colorimetric bacterial detection (BacT/ALERT® Culture Media, BioMérieux, France). The bottles contain activated charcoal to neutralise antimicrobials and make for a more accurate diagnosis[40]. They also make it possible to perform an antibiotic sensitivity test.

2.1.3 Statistical analysis

Categorical variables were presented as means and ranges as percentages. When two related items of data were analyzed, the Chi-square or Fisher exact test was used. In all cases, a p value of <0.05 was considered statistically significant. A power analysis was performed to ensure an adequate sample size for the study. Selecting an incidence of infection of 1 %, a significance level (α) of 0.05 and a power (β) of 80 %, the sample size needed was 119 patients in each group. The statistical analysis was done using the SPSS 18.0 (SPSS Inc., Chicago, IL) statistical package.

2.2 Second study

Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated.

In the second study, a prospective controlled study was performed. The study was approved by the Ethics Committee. All patients operated on for ACL-R in 3 university hospitals were included. Those patients that needed an extraarticular procedure or those who received an allograft were

excluded from the study. Patients with previous knee surgeries or previous knee punctures were also excluded. The patients were operated on between June 2016 and December 2016.

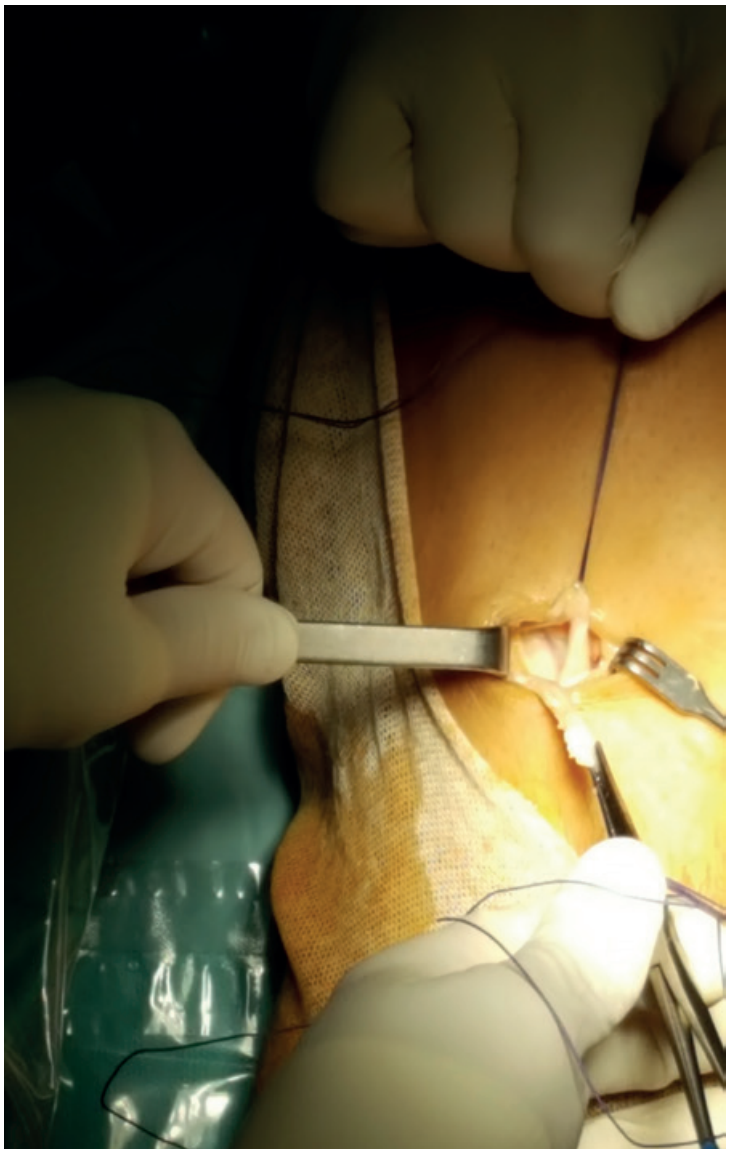
During the study period, a total of eighty-seven ACL-R were initially included in the study. Thirty-seven out of those 87 patients were excluded because they did not meet the inclusion criteria. Thus, 50 patients were included for the present study and there were no further losses.

2.2.1 Surgical protocol

The surgical protocol was similar to the one in the first study. A quadrupled hamstrings autograft or bone-patellar tendon-bone (BPTB) autograft was chosen depending on the patients' characteristics and surgeons' preferences. All operations were performed on an outpatient basis. Therefore, no drains were used after surgery. The prophylactic antibiotic protocol consisted of a single dose of 2 g of preoperative IV cefazolin or a single dose of 1 g of preoperative IV vancomycin if a type 1 penicillin allergy had been reported. As a part of the usual protocol, the ACL graft is always soaked in a vancomycin solution of 5 mg/ml. The solution was prepared by mixing 100 ml of sterile saline with 500 mg of vancomycin powder in a tray. After obtaining and preparing the graft, it was immersed in the tray and then it was wrapped in gauze that had been saturated with the vancomycin solution beforehand. The graft was left there for 10-15 minutes immediately prior to its use in the ACL-R.

2.2.2 Source of samples

Three samples were taken from each ACL graft at 3 distinct points in time. The first sample (sample 1) was obtained immediately after graft harvesting.

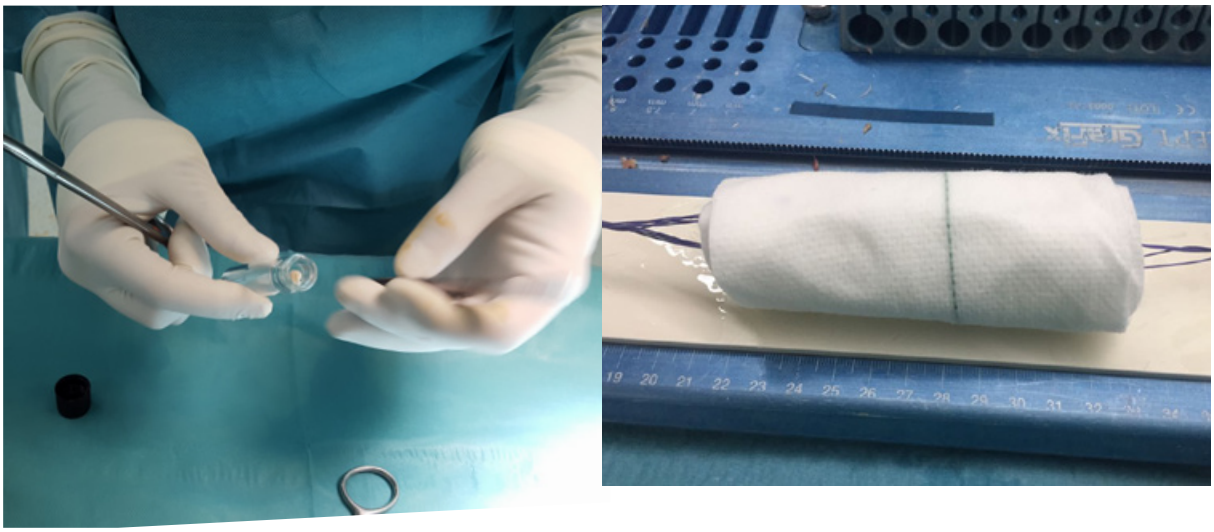


Picture 1. Sample one was taken right after graft harvesting.

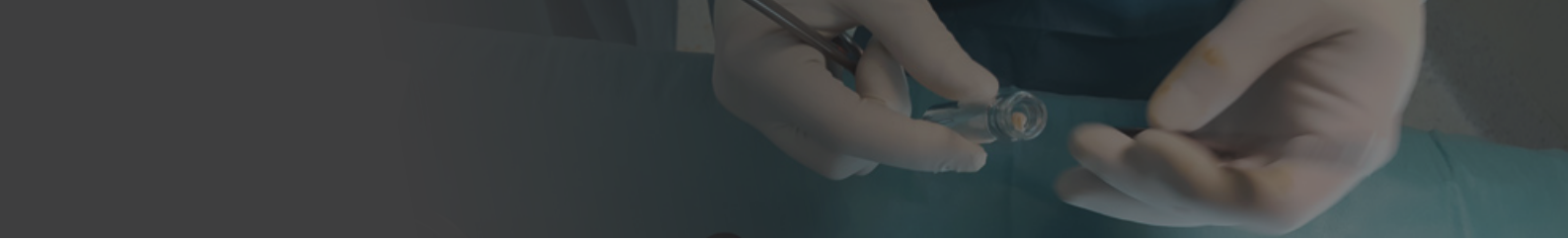
After graft preparation, the remaining tissue was divided into two parts: one of them was tagged as the second sample (sample 2) and the remaining tissue was soaked in the vancomycin solution with the graft that was to be implanted (sample 3).

Picture 2. After preparation, the remaining tissue was separated into two parts.

A minimum sample size of 1-3 mm^3 was requested in all cases to allow for further analysis.



Picture 3. After preparation, one half of the tissue was sent without any treatment (sample 2, left picture). The other half was wrapped in gauze with the vancomycin solution (sample 3, right picture)



2.2.3 Microbiological protocol

Each tissue sample was sent in separate sterile containers to the microbiological department. All cultures were incubated at 37 ºC with 5% CO2 in agar plates for 7 days (aerobically) or 14 days (anaerobically) and inspected daily for microbial growth. Any bacterial growth and the number of colony forming units were reported. Strain identification and a susceptibility test were performed by using standard microbiological techniques. After study completion, each positive culture was re-evaluated by an experienced microbiologist specialized in orthopedic related infections.

2.2.4 Statistical analysis

Continuous variables were presented as means (with standard deviation, SD) and ranges as percentages. Categorical data was compared between groups with the Chi-Square Test. A p value under 0.05 was considered statistically significant.

The Chi-Square Difference Test was used to determine the sample size. It was assumed that there would be 17% contamination in group sample 1 and group sample 2 (as previously reported by Badran[38]) and 0% contamination in group sample 3. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 50 subjects were necessary to recognize a difference consisting in an initial proportion of 0.17 and a final proportion of 0 as statistically significant. A drop-out rate of 5% was anticipated.

The statistical analysis was done using the SPSS Statistics 18.0 software package (SPSS Inc., Chicago, IL).

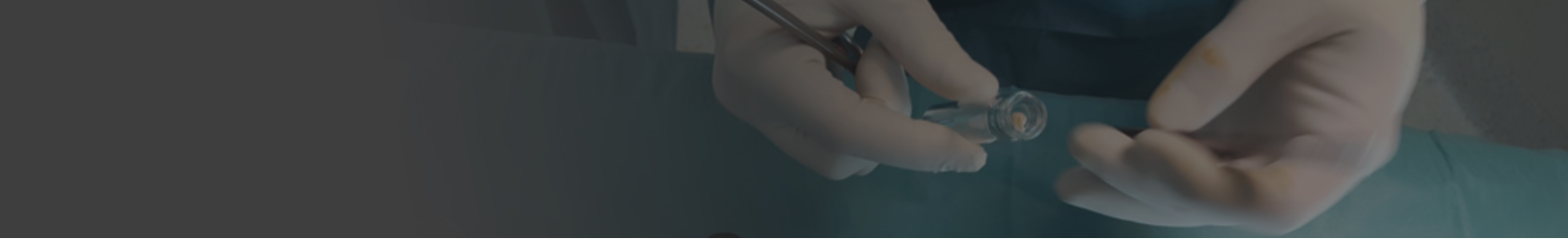
2.3 Third study

Infections after Anterior Cruciate Ligament Reconstruction: Which Antibiotic after Arthroscopic Debridement?

A retrospective review of all the patients who consecutively underwent primary arthroscopic ACL-R with an autograft in two University Hospitals was performed. Those patients who needed an extra-articular procedure or those who received an allograft were not included in the study. Patients were operated on between January 2006 and December 2009. All patients were operated on by the same surgical team composed of four senior surgeons. All operations were performed on an outpatient basis. The prophylactic antibiotic protocol consisted of a single dose of 2 g of preoperative intravenous (IV) cefazolin. If a penicillin allergy was reported, a single dose of 1 g of preoperative IV vancomycin was administered. No patient in this series informed of having an allergy to vancomycin. The types of graft employed were a quadrupled hamstrings and a bone–patellar tendon–bone (BPTB). No drains were left after surgery.

2.3.1 Diagnostic Criteria for Septic Arthritis

Diagnosis of septic arthritis was based on the patients' anamnesis, physical examination, laboratory parameters, and cultures of synovial fluid and/or joint tissue. Synovial aspiration was performed as soon as the diagnosis was suspected. The liquid obtained was immediately sent for biochemical analysis and cell count analysis in heparin tubes. The remaining synovial fluid was introduced into aerobic and anaerobic blood culture bottles for automatic colorimetric bacterial detection (BacT/ALERT Culture Media, BioMérieux, Marcy-l'Étoile, France). These bottles contain activated charcoal to neutralize antimicrobials and make for a more accurate diagnosis.



2.3.2 Surgical Approach

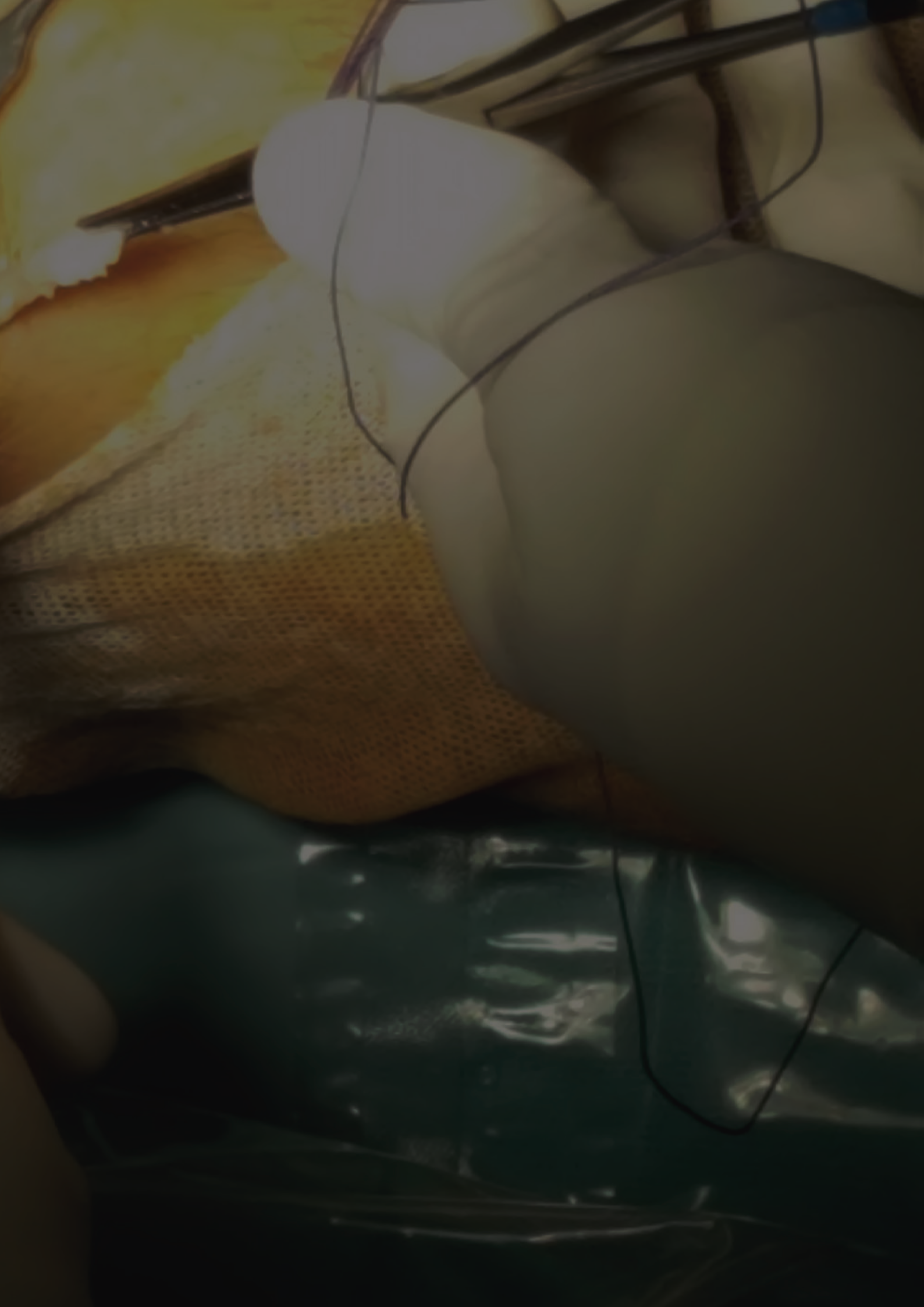
When an ACL-R infection was confirmed or highly suspected, an arthroscopic lavage was performed as soon as possible and tissue samples were taken. ACL graft indemnity was evaluated. It was not removed when it was considered viable and well fixed. An empiric IV antibiotic regimen (vancomycin plus ceftazidime) was started until the cultures results were available.

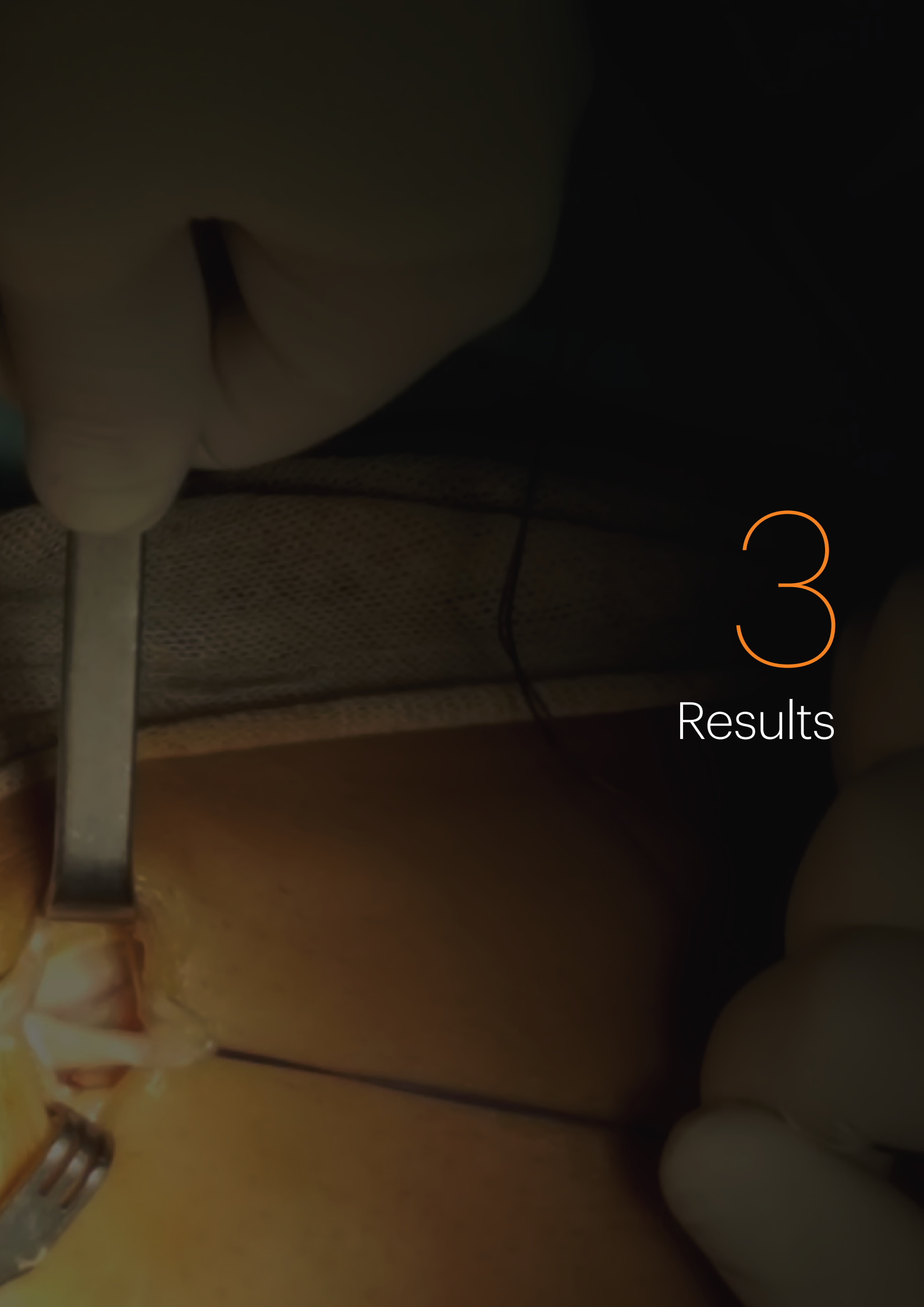
2.3.3 Criteria for Infection Healing

At a minimum 2-year follow-up, the infection was considered cured with a normal C-reactive protein (CRP) level and a correctly functioning and pain-free knee. Functional outcome measures were previously reported and do not constitute the core of the current work. The functional assessment included a detailed physical examination (including the pivot-shift and Lachman tests), an arthrometric evaluation with KT-1000 (MEDmetric, San Diego, CA), functional scores (modified Lysholm and Gillquist scoring scale), the International Knee Documentation Committee (IKDC) form), and radiographic evaluation (standard anteroposterior and lateral views as well as Rosenberg view). In the radiological evaluation, osteophyte formation and either medial or lateral joint space narrowing were assessed.

2.3.4. Statistical Analysis

Continuous variables are expressed as mean and standard deviations (or ranges) and categorical variables were presented as means and percentages. When two related items of data were analyzed, the chi-square or Fisher exact test was used. In all cases, a p-value of less than 0.05 was considered statistically significant. The statistical analysis was done using the SPSS 18.0 (SPSS Inc., Chicago, IL) statistical package.





3
Results

Results

3.1 First study

Autograft soaking in vancomycin reduces the risk of infection after anterior cruciate ligament reconstruction.

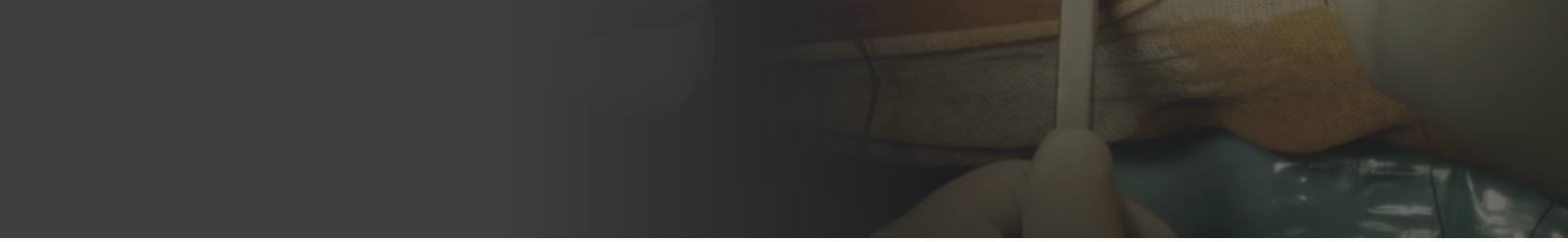
There were 1,544 patients who met the inclusion criteria. The first 810 were included in group 1, and the following 734 were included in group 2. Both groups were similar in terms of age, sex and BMI (n.s.).

3.1.1 Surgical data

The type of graft employed was a quadrupled hamstring in 84 % of the cases and BPTB in 16% of cases. BPTB grafts were fixed using a resorbable interference screw in both sides, in all cases. The Biosteon® screw (Stryker, Kalamazoo, MI, USA) was used in the first 151 BPTB cases, and the GENESYS™ Matryx® Interference Screw (ConMed Linvatec, Largo, FL, USA) was employed in the last 96 cases. In the first 607 cases of hamstring grafts, the femoral fixation was carried out with the Cross-Pin system® (Stryker) and with a resorbable interference screw (Biosteon®, Stryker Endoscopy, USA) for the tibial fixation. In the succeeding 690 cases of hamstrings grafts, the graft was fixed at the femoral side using the XO Button Fixation System® (ConMed Linvatec), while a resorbable GENESYS™ Matryx® Interference Screw (ConMed Linvatec) was used for tibial fixation.

3.1.2 Infection cases analysis

There was an overall infection rate of 0.97% (15 cases) after ACLR. All cases were acute infections that developed in the early post-operative period (1–5 weeks after surgery). All 15 infections occurred in group 1 (only intravenous antibiotic prophylaxis without vancomycin saturation of the graft), which represents an infection rate of 1.85% (15 out of 810). Within this group of patients that developed an infection, a partial meniscectomy was performed in two cases and a bucket-handle tear of the medial meniscus was sutured in another patient. The bacteria isolated were as follows: 13 Staphylococcus species (87%) of which 10 were CNS (67%) and



3 Staphylococcus aureus (20%). There was also an infection due to Propionibacterium acnes and one culture-negative infection. One of the patients needed graft removal and a 2-stage ACLR procedure because of treatment failure after the third arthroscopic debridement and lavage. There was no infection among patients who received systemic antibiotic prophylaxis and graft presoaking with vancomycin (group 2). This represented an infection rate of 0% (0 out of 734). Statistical analysis showed that prior saturation of the ACL graft in a vancomycin solution significantly reduced the infection rate ($p<0.001$) in comparison with patients on whom this technique was not performed.

3.2 Second study

Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated.

There were 26 men and 24 women and the mean age of the sample was 36.2 years old (SD 11.4 years old). In 29 patients, an autologous BPTP was used and 21 were treated with

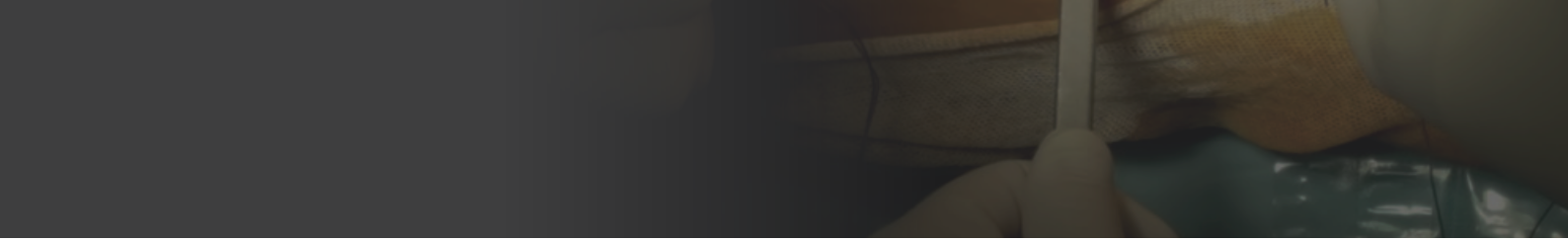
autologous quadrupled hamstrings. No differences in terms of contamination were observed when hamstring and BPTB grafts were compared (p=0.684). None of the patients developed septic arthritis in this series.

3.2.1 Contamination during harvesting and manipulation

In 7 cases (14%), either sample 1 or sample 2 were positive. In 5 cases (10%), only the sample after graft harvest and preparation was positive (sample 2). In 2 cases (4%), sample 1 and sample 2 were positive for the same bacteria. Isolated microorganisms corresponded to coagulase-negative staphylococci (CNS) and *Propionibacterium acnes*. More data about those 5 cases can be seen in table 1.

Table 1. Details of the 7 cases with positive samples

Hospital number	Age	Sex	Graft Type	Sample 1	Sample 2	Sample 3
1	34	Male	BPTB	Negative	*S. epidermidis*	Negative
1	27	Female	Hamstrings	Negative	*P. acnes*	Negative
2	18	Male	BPTB	Negative	*S. epidermidis*	Negative
2	51	Male	Hamstrings	Negative	*S. Lugdunensis*	Negative
3	26	Female	BPTB	Negative	*S. epidermidis* / *S. auricularis*	Negative
1	56	Male	BPTB	*P. acnes*	*P. acnes*	Negative
1	55	Female	BPTB	*S. caprae*	*S. caprae*	Negative



3.2.2 The effect of vancomycin soaking on contamination

No bacterial growth was observed in sample 3 ($p<0.001$). Thus, none of those 7 positive cases (0%) was positive after vancomycin soaking ($p<0.001$).

3.3 Third study

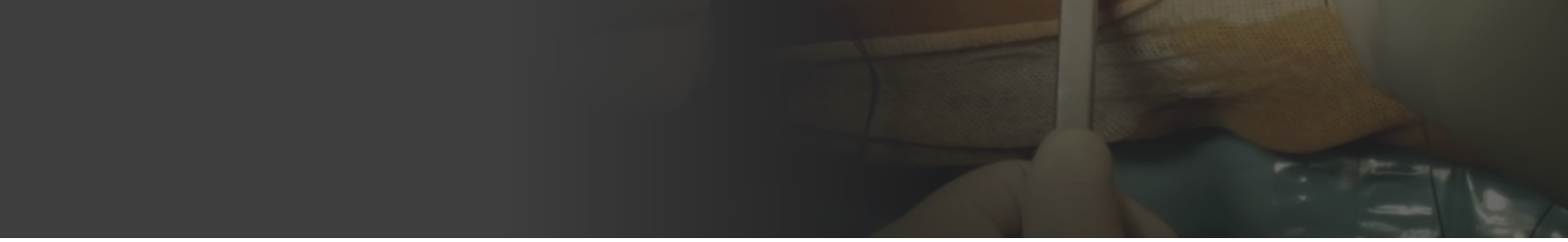
Infections after Anterior Cruciate Ligament Reconstruction: Which Antibiotic after Arthroscopic Debridement?

There were 810 patients who underwent ACLR during the inclusion period, of which 112 were women (13.8%) and mean age was 33.5 years (SD 7.6). There were 15 ACLR infections (1.8%). The statistical analysis did not show any difference between the infection group and the rest of the sample in terms of age, sex, and body mass index ($p > 0.05$). All of the cases were acute infections that occurred in the early postoperative period. The isolated bacteria were as follows: 13 Staphylococcus species (86.6%) of which 10 (66.6%) were CNS and 3

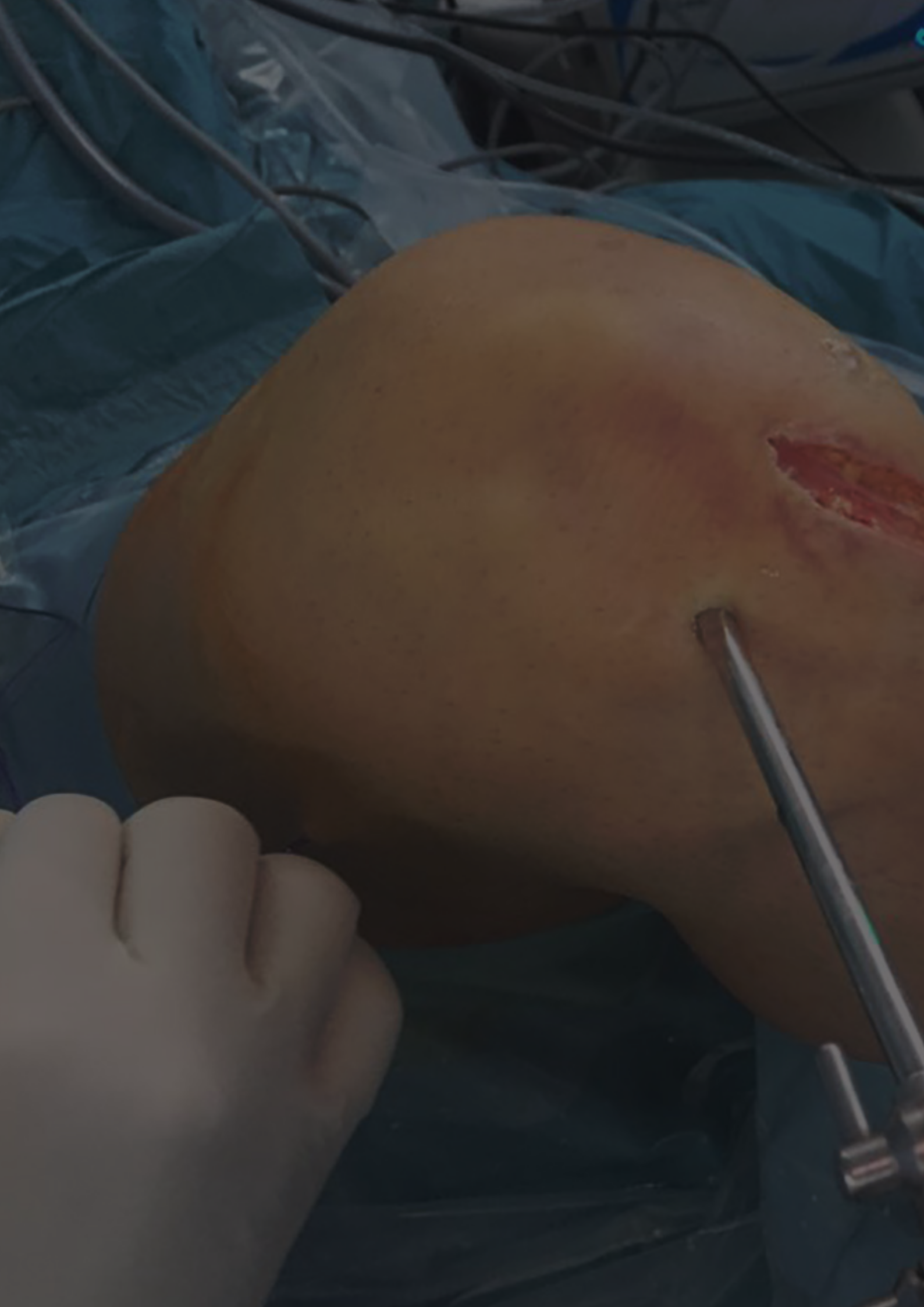
Staphylococcus aureus (20%). There was 1 infection due to P. acnes and 1 culture negative infection. Among the 13 staphylococcal cases (86.6%), 10 were susceptible to both quinolones and rifampicin (76.9% of the staphylococcal infections). In two cases, the microorganisms were rifampicin resistant. In the one remaining case, the CNS was resistant to quinolones. Alternative antibiotic treatment in those resistant cases can be seen in Table 2.

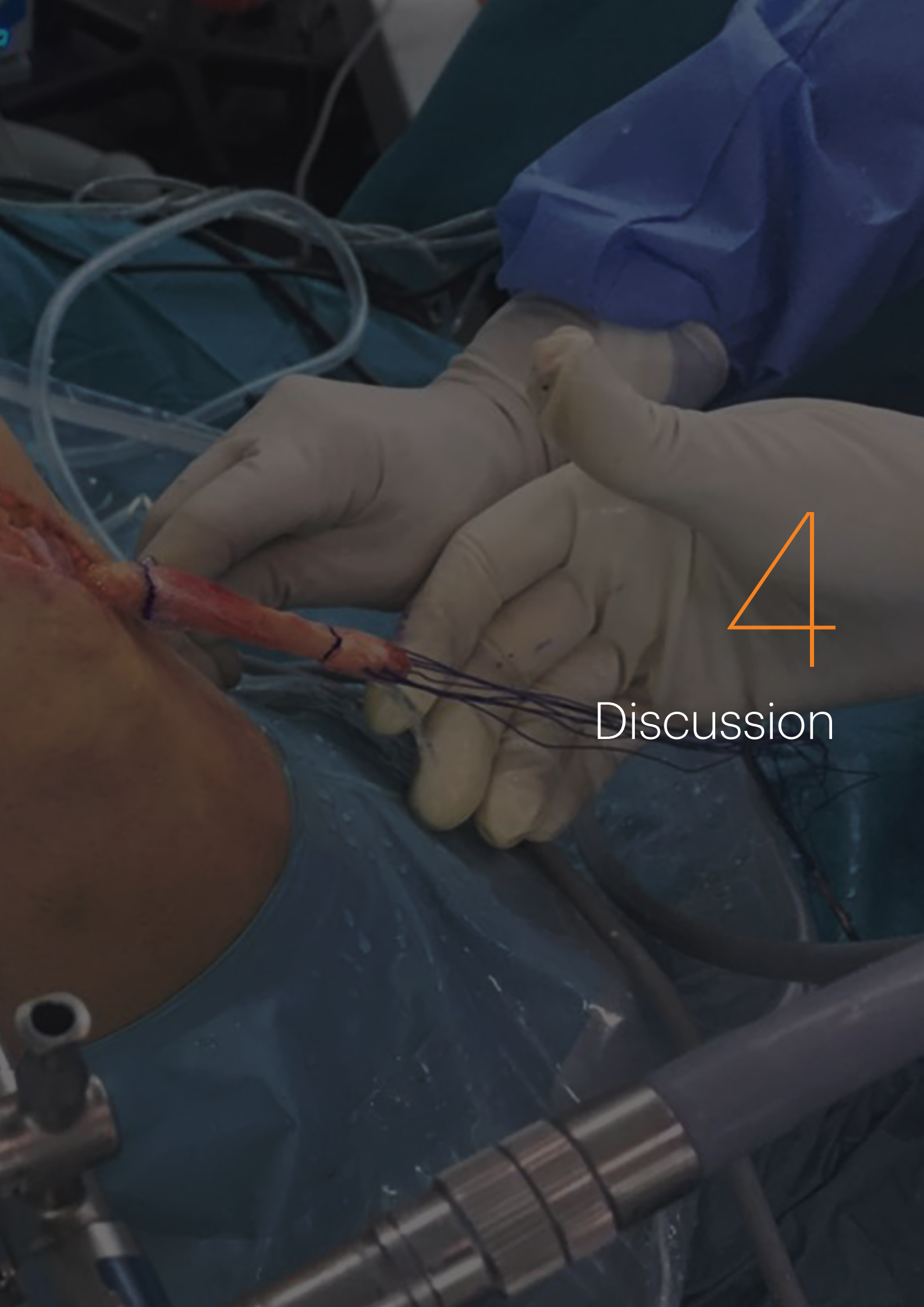
Table 2. Details of the 14 infected cases

CASE	ACL graft	Micro-organism	Antibiotic	CRP** at end follow-up	Number of arthroscopic lavages	Antibiotic therapy duration (weeks)
1	Hamstring	S. aureus	Levofloxacin + Rifampicin	0.4	*1*	8
2	Hamstring	MRSA	Levofloxacin + Rifampicin	0.6	*2*	6
3	Patellar tendon	Propionibacterium acnes	Amoxicillin + Clavulanic Acid	0.5	*1*	6
4*	Hamstring	CNS	Linezolid + Rifampicin	0.2	*3*	6
5	Hamstring	CNS	Levofloxacin + Rifampicin	0.2	*1*	6
6	Patellar tendon	CNS	Co-trimoxazole + Rifampicin	*0.2*	*2*	6
7	Hamstring	CNS	Levofloxacin + Rifampicin	*0.2*	*2*	5
8	Hamstring	CNS	Ciprofloxacin + Rifampicin	0.9	*1*	6
9	Hamstring	S. aureus	Ciprofloxacine	0.9	*1*	4
10	Hamstring	Unknown	Amoxicillin + Clavulanic Acid	0.2	*1*	6
11	Hamstring	CNS	Levofloxacin + Rifampicin	0.6	*1*	6
12	Hamstring	CNS	Levofloxacin + Rifampicin	*0.5*	*1*	6
13	Hamstring	CNS	Levofloxacin + Rifampicin	*0.2*	*1*	6
14	Hamstring	CNS	Levofloxacin	*0.2*	*1*	6



It is of remarkable interest that one of the quinolones- and rifampicin-susceptible CNS was treated with linezolid and rifampicin. This was the only case in which the graft had to be removed and needed a two-stage ACLR procedure due to treatment failure after the third arthroscopic debridement and lavage (persisting pain and purulent drainage). One of the staphylococcal cases was due to methicillin-resistant S. aureus. Even in this case, the antibiotics of choice were levofloxacin and rifampicin and they produced a good outcome. Antibiotic treatment lasted a median of 6 weeks (empirical treatment intravenously delivered plus orally directed therapy). Oral treatment started as soon as the culture results were available. No side effects were reported in patients treated with quinolones and rifampicin. In all but one patient (the one who needed graft removal), CRP levels returned to normal at a mean of 3 weeks without local symptoms. Function and pain improved, although these patients never reached functional scores like those patients without infection.





4

Discussion

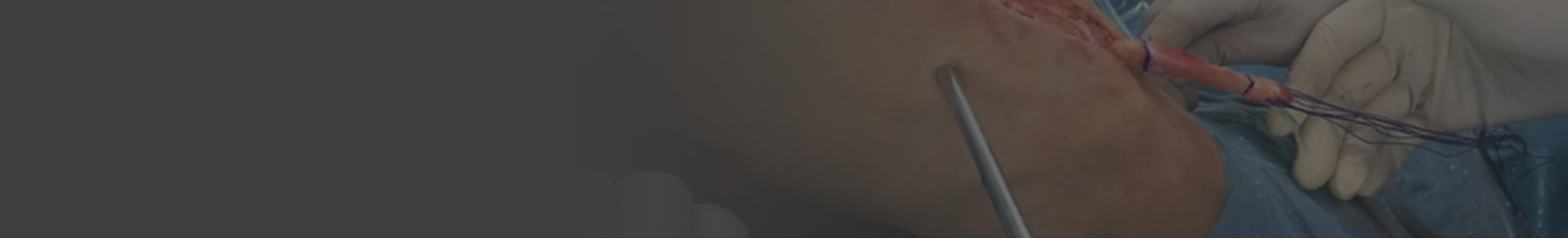
Discussion

The main finding of the first study is that the solution of 5 mg/dl of vancomycin reduces the incidence of infection after ACL-R when the ACL graft is soaked in the vancomycin solution. This finding is backed up by the results obtained in the second study. A contamination rate of 14% was observed during the graft harvesting and preparation process but the vancomycin solution of 5 mg/dl completely eradicates this contamination. Finally, the third study's results suggest that the anti-biofim antibiotic treatment used in PJI can achieve a high cure rate in ACL-R infections when it is combined with arthroscopic debridement.

More than 90% of ACL-R infections are acute infections[29]. The literature published on ACL-R infections' etiology points out that CNS is the most frequent microorganism isolated. S. aureus and GNB can be also found[36]. There is no explanation as to why non-virulent microorganisms are responsible for the great majority of acute infections. One theory was the presumed contamination that can occur in the harvesting and preparation process. There are several studies that describe the accidental contamination of the ACL graft during the preparation course[38,41–44]. The results they obtained are consistent with those presented in this thesis. Moreover, the most frequent bacteria isolated in those contamination studies are CNS, which is also the causative agent reported on clinical studies. Even though the results presented in this thesis cannot completely affirm that the origin of ACL-R infections is in contamination during preparation, these results provide strong evidence to support that theory.

Another finding obtained in the second study is that the contamination that was observed was completely eradicated by using a vancomycin solution of 5 mg/dl. This was the very first study that used a vancomycin solution to eliminate the bacteria. There are other studies that used other antibiotics or other antiseptic solutions. However, they can do harm to osteocytes or tenocytes[45,46].

The clinical confirmation that the 5 mg/dl vancomycin solution reduces the infection rate was validated in the first study as a reduction from an incidence of 1.8% to 0% was observed. This finding was also observed by Vertullo et al. using the same technique[37,47]. There could be two



explanations for this outcome. The first one is that the eradication of contamination occurred during harvesting and preparation, as was proven in the second study in this thesis. The other is that graft soaking in the solution provides a reservoir of vancomycin that is released over 48 hours and is over the minimal inhibitory concentration (MIC) for most bacteria as proven by Grayson et al.[48]

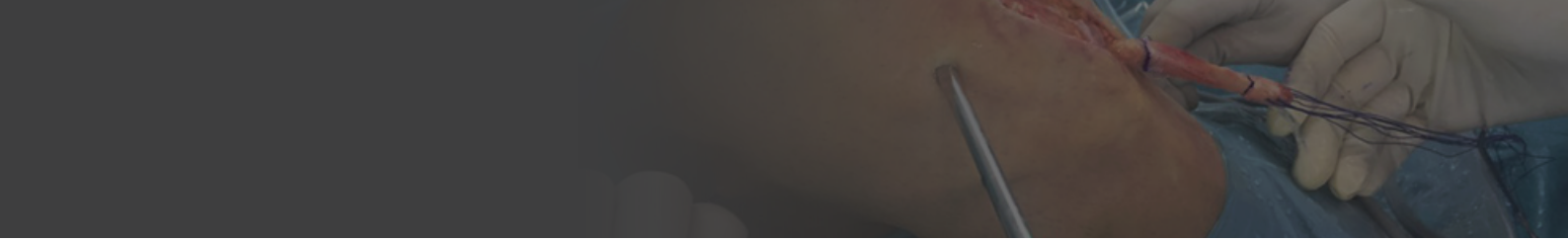
Finally, the third study was focused on treatment management after ACL-R infections. There is high-quality evidence that surgical debridement can be performed arthroscopically[29,34,49,50]. The reasoning that may explain this difference with PJI is that the popliteal fossa can easily be reached by means of the scope when there is no prosthesis. Another reason could be the minor quantity of biofilm as the foreign body is smaller than the prosthesis and therefore debridement can be achieved with a less aggressive technique.

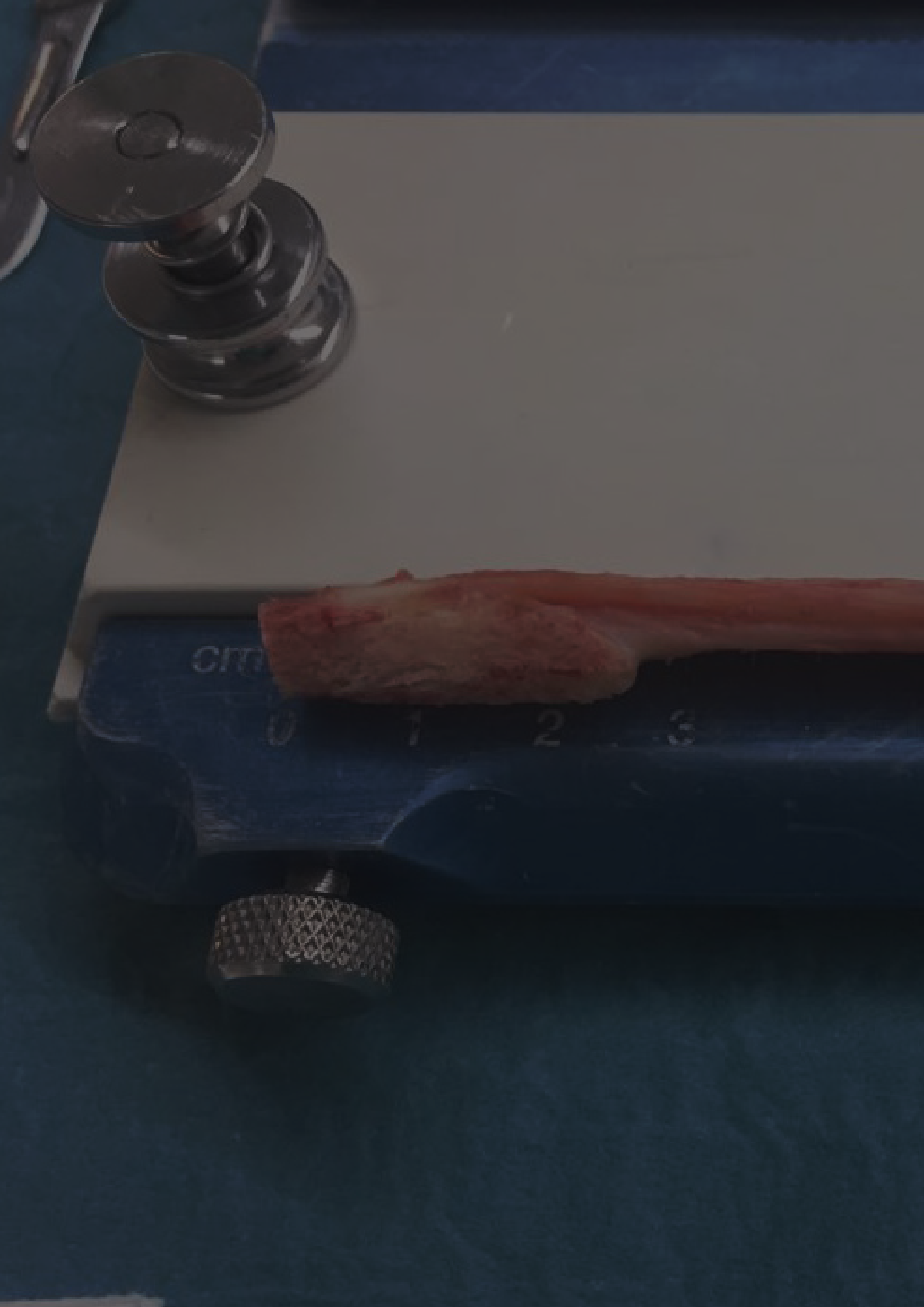
In the third study, arthroscopic debridement was combined with antibiotic treatment to achieve infection cure. Contrariwise to surgical management, antibiotic treatment has not been well assessed. The third study of the present thesis was the first ever study that reported the specific antibiotic treatment used in ACL-R infections. The rationale that was applied was an extrapolation of antibiotic treatment in PJI[51]. Clinical trials on staphylococcal PJI confirmed that rifampicin acts as an antibiofilm agent that can kill not only planktonic bacteria but also the dormant ones[27]. Therefore the infected foreign body can be left in place and a complete hardware and graft removal is no longer necessary. It is important to remember that rifampicin should never be used in monotherapy as resistance always emerges[52]. Quinolones have proven to be a perfect match to combine with rifampicin for its high bio-availability as clinical studies have reported high cure rates with this combination[53].

When this antibiotic treatment was extrapolated to staphylococcal ACL-R infections, a cure rate of 100% was observed when it was combined with arthroscopic debridement. One difference with PJI is the shorter treatment duration that was applied as a total period of 6 weeks of antibiotic treatment was enough to achieve infection healing.

Discussion

Several limitations should be considered in the present thesis and its compendium of studies. The first study has a retrospective design with a lack of randomization. On the other hand, the fact that some steps in the surgical technique changed during the study period, such as the location of the femoral tunnel, may produce a bias. Regardless of this variation in the fixation system in the femur, no data suggested that the decrease in the rate of infection after ACLR could be attributed to the change of fixation. For the second study, the most important limitation is the practical correlation of contamination with infection. However, the bacteria that have been identified are the same as those found in clinical practice. Another limitation might be the fact that three different microbiology departments analyzed the samples. However, an experienced microbiologist specialized in orthopedic-related infections reviewed the positive samples to reduce this possible bias. The small cohort of patients could be considered another limitation, but a sample size calculation was made beforehand. The third and last study can be considered as the one with more important limitations. First, the retrospective design of the study and the lack of a control group make it difficult to know whether other treatments would be as effective as the one presented here. Then, there is the small number of patients even though it is the largest series described in the literature, to the best of our knowledge.





5 Conclusions

Conclusions

5.1 First study

1 STUDY

Autograft soaking in vancomycin reduces the risk of infection after anterior cruciate ligament reconstruction.

Autograft presoaking with vancomycin in combination with classical intravenous antibiotic prophylaxis reduces the rate of knee joint infection following an ACL-R in comparison with antibiotic prophylaxis alone.

5.2 Second study

2 STUDY

Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated.

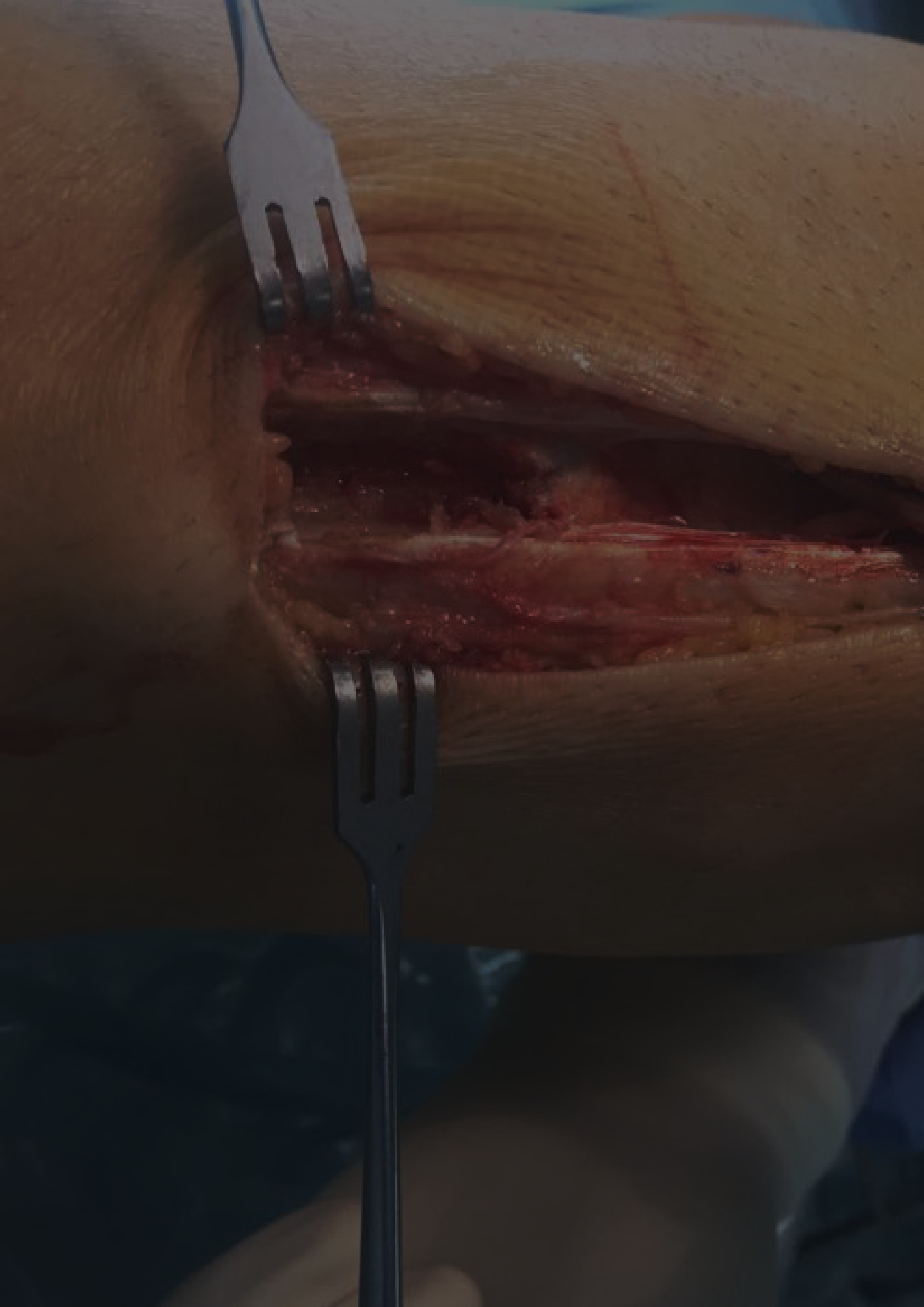
The harvesting and processing of ACL grafts causes bacterial contamination in 14% of all cases. This contamination is fully eradicated after soaking the grafts in the vancomycin solution.

5.3 Third study

3 STUDY

Infections after Anterior Cruciate Ligament Reconstruction: Which Antibiotic after Arthroscopic Debridement?

Oral antibiotic treatment with levofloxacin and rifampicin for a period of 6 weeks should be considered as the treatment of choice in acute staphylococcal ACL-R infections with a retained graft after arthroscopic debridement.



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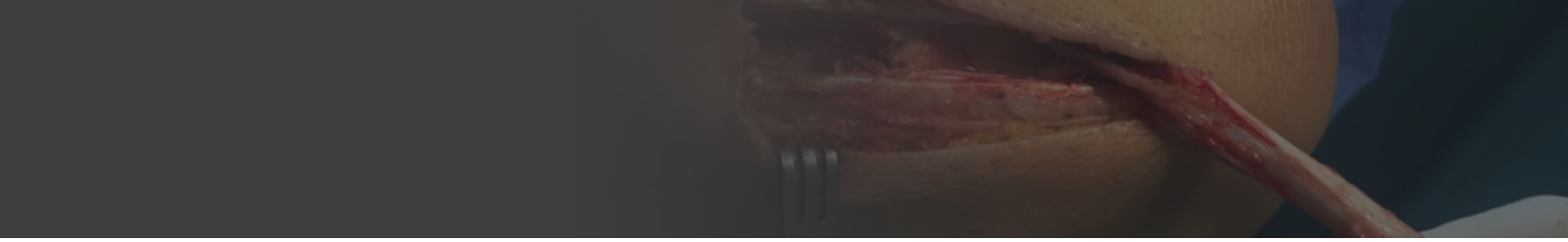

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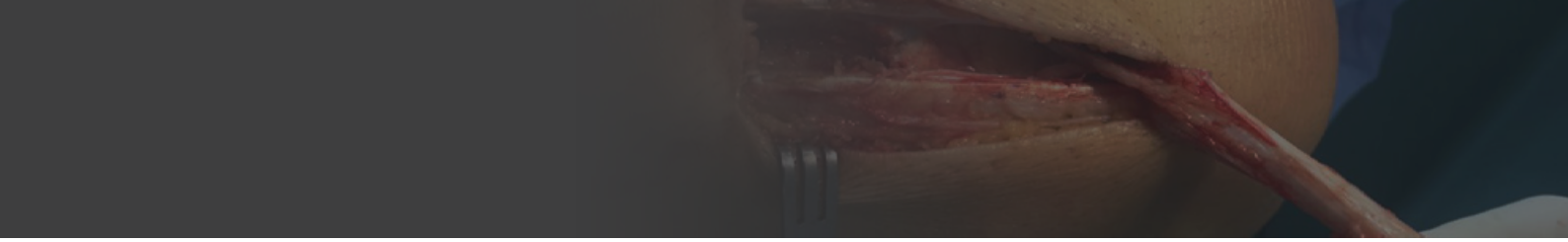

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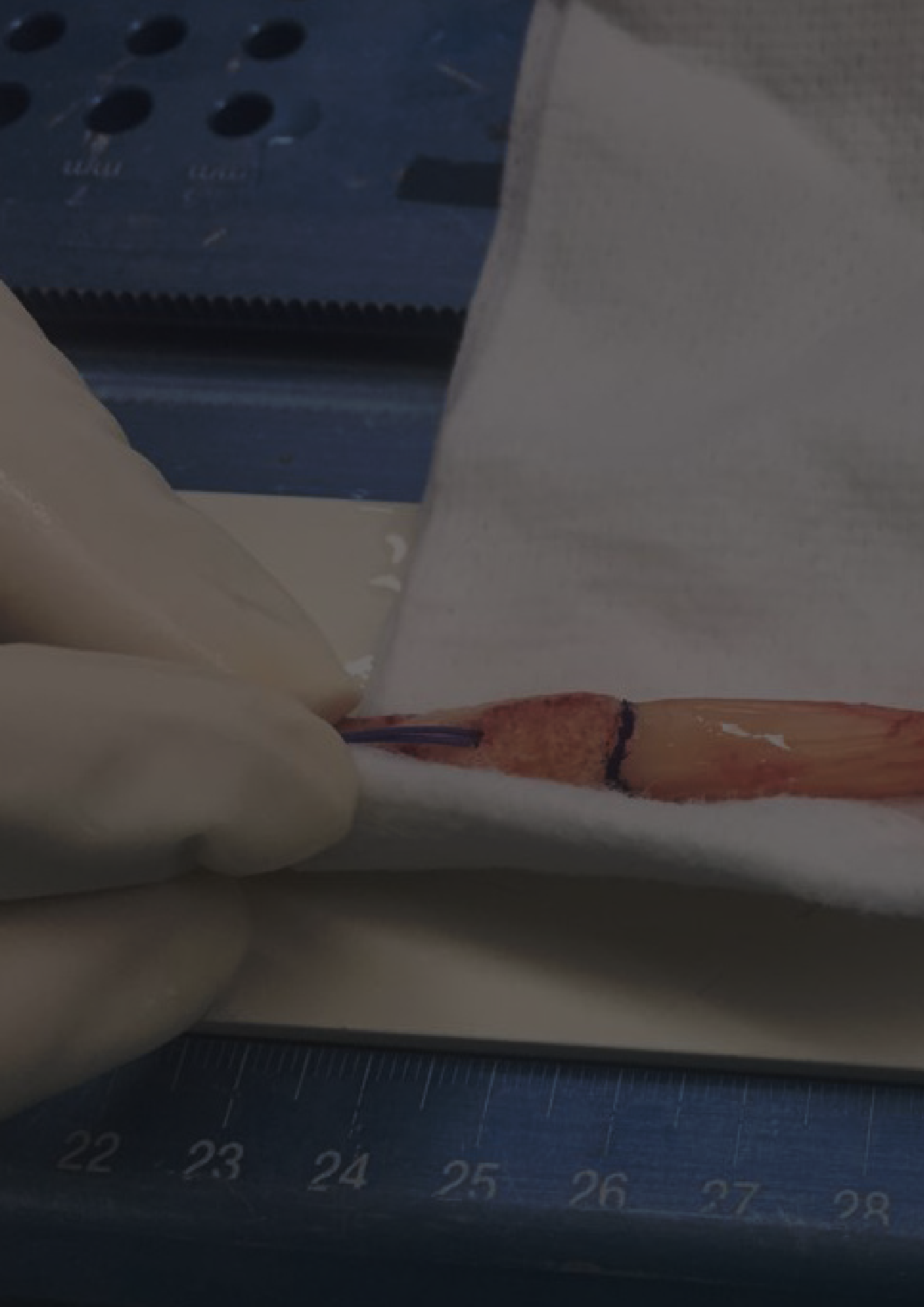
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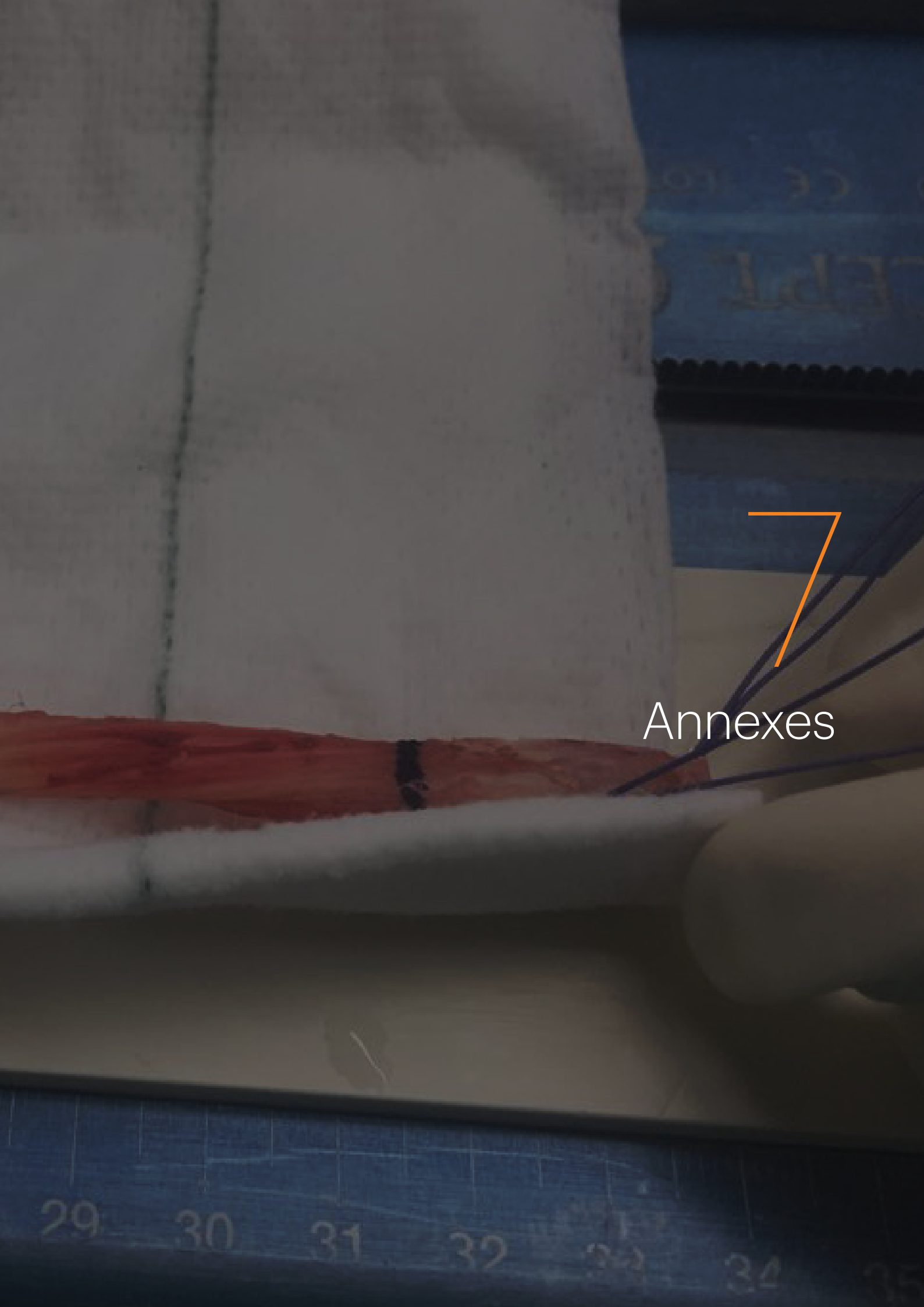

7 Annexes

WORK 1

Knee Surg Sports Traumatol Arthrosc
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KNEE

Autograft soaking in vancomycin reduces the risk of infection after anterior cruciate ligament reconstruction

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Abstract
Purpose To determine whether the bathing of an anterior cruciate ligament (ACL) autograft in vancomycin reduces the rate of infection following an ACL reconstruction.
Methods Retrospective analysis of all ACL reconstructions over an 8-year period in two University Hospitals. In the initial 4-year period, all patients were operated on under classical antibiotic intravenous prophylaxis (group 1). Over the last 4-year period, this prophylaxis was supplemented with presoaking of the autograft (group 2). Presoaking was performed with sterile gauze previously saturated with a vancomycin solution (5 mg/ml).
Results There were 810 and 734 patients in group 1 and 2, respectively. Fifteen cases of knee joint infections were identified in the series (0.97 %). All of these infections occurred in group 1, representing a rate of infection of 1.85 % in comparison with 0 % in group 2 ($p < 0.001$).
Conclusions Autograft presoaking with vancomycin in combination with classical intravenous antibiotic prophylaxis reduced the rate of knee joint infection following an ACLR in comparison with antibiotic prophylaxis alone. This technique could be of relevance in daily clinical practice to prevent infection after ACLR.
Level of evidence Case control study, retrospective comparative study, Level III.

Keywords Anterior cruciate ligament · Antibiotic prophylaxis · Vancomycin · Knee infection · Biofilm

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Introduction

Septic arthritis following an anterior cruciate ligament reconstruction (ACLR) is a serious but uncommon complication, with the incidence rate ranging from 0.14 to 1.8 % [6, 14, 16]. A hamstring autograft [4, 12, 15], concomitant open surgical procedures [20], the use of drains [26] or previous surgery on the same knee [3, 12, 19] have been related to a higher risk of suffering a knee joint infection after an ACLR.

Staphylococci are the most important causative agents in up to 90 % of cases. Approximately half of those are due to coagulase-negative staphylococci (CNS) [6, 13, 15, 20, 21, 23, 26]. Other pathogens reported are *Propionibacterium acnes* and *Enterobacter* species [6]. Some authors have linked this high percentage of CNS to the graft harvest and its contamination with patients' skin bacteria [6].

The use of a preoperative prophylactic antibiotic [24] as well as a proper hair removal, in the cases which needed it [22], has demonstrated efficiency in reducing the rate of infection in orthopaedic procedures. Recently, autograft presoaking with vancomycin has been described as showing promising results in decreasing the rate of infection following an ACLR [25], although they only used hamstrings grafts in the study.

In a study published by Torres-Claramunt [23], the rate of infection in the patients operated on for an ACLR was assessed. This rate (1.8 %) was higher than initially expected. Therefore, presoaking of the autograft with vancomycin was introduced as a new prophylactic measure in the ACLR in order to reduce this rate of infection.

The purpose of this study was to find out whether the implementation of prophylactic graft saturation with vancomycin reduces the rate of infection following an ACLR, using either hamstrings or bone–patellar tendon–bone (BPTB) grafts. The initial hypothesis was that prophylactic autograft presoaking in vancomycin along with a prophylactic intravenous (IV) antibiotic reduces the incidence of infection after ACLR.

Materials and methods

A retrospective review of all the patients that consecutively underwent primary arthroscopic ACLR with an autograft in two University Hospitals was performed. Those patients who needed an extra-articular procedure or those who received an allograft were not included in the study. In the initial 4-year period, the patients received preoperative IV antibiotics (group 1). In the following 4-year period, the patients received preoperative IV antibiotics and, furthermore, the graft was presoaked in a vancomycin solution (group 2).

Surgical technique

All patients were operated on by the same surgical team composed of four senior surgeons. All operations were performed on an outpatient basis. The prophylactic antibiotic protocol consisted in a single dose of 2 g of preoperative IV cefazolin or a single dose of 1 g of preoperative IV vancomycin, if a penicillin allergy was reported [24]. No patient in this series informed of a vancomycin allergy. The types of graft employed were a quadrupled hamstrings and a BPTB. A pretension of 80 N was applied for 5 min before fixation of the hamstrings grafts. BPTB grafts were fixed using a resorbable interference screw in both sides. The hamstring grafts femoral fixation was carried out either with a transversal fixation (Cross-Pin system®, Stryker, Kalamazoo, MI, USA) or with a cortical suspensory fixation system (XO Button Fixation System®, ConMed Linvatec, Largo, FL, USA). Tibial fixation was accomplished with a resorbable interference screw. No drains were left after surgery.

The technique of vancomycin saturation has been performed as previously described by Grayson et al. [10]. A solution of 100 ml of sterile saline was prepared in a tray and mixed with 500 mg of vancomycin powder. When the graft was obtained and prepared, it was immersed in the tray and then it was wrapped in gauze that had been saturated with this vancomycin solution beforehand. The graft was left there for 10–15 min (until it was used for the ACL reconstruction).

Diagnostic criteria for septic arthritis

Diagnosis of septic arthritis was based on patients' anamnesis and physical examination, laboratory parameters and cultures of synovial fluid and/or joint tissue. Synovial aspiration was performed as soon as the diagnosis was suspected. The liquid obtained was immediately sent for biochemical analysis and cell count analysis in heparin tubes. The remaining synovial fluid was introduced into aerobic and anaerobic blood culture bottles for automatic colorimetric bacterial detection (BacT/ALERT® Culture Media, BioMérieux, France). These bottles contain activated charcoal to neutralise antimicrobials and make for a more accurate diagnosis. They also make it possible to perform an antibiotic sensitivity test.

Statistical analysis

Categorical variables were presented as means and range as percentages. When two related items of data were analysed, the Chi-square or Fisher exact test was used. In all cases, a p value of <0.05 was considered statistically significant. A power analysis was performed to ensure an adequate sample size for the study. Selecting an incidence of infection of 1 %, a significance level (α) of 0.05 and a power (β) of 80 %, the sample size needed was 119 patients in each group. The statistical analysis was done using SPSS 18.0 (SPSS Inc., Chicago, IL) statistical package.

Results

There were 1,544 patients who met the inclusion criteria. The first 810 were included in group 1, and the following 734 were included in group 2. Both groups were similar in terms of age, sex and BMI (n.s.).

Surgical data

The type of graft employed was a quadrupled hamstring in 84 % of the cases and BPTB in 16 % of cases. BPTB grafts were fixed using a resorbable interference screw in both sides, in all cases. The Biosteon® screw (Stryker, Kalamazoo, MI, USA) was used in the first 151 BPTB cases, and the GENESYS™ Matryx® Interference Screw (ConMed Linvatec, Largo, FL, USA) was employed in the last 96 cases. In the first 607 cases of hamstring grafts, the

femoral fixation was carried out with the Cross-Pin system® (Stryker) and with a resorbable interference screw (Biosteon®, Stryker Endoscopy, USA) for the tibial fixation. In the succeeding 690 cases of hamstrings graft, the graft was fixed at the femoral side using the XO Button Fixation System® (ConMed Linvatec), while a resorbable GENESYS™ Matryx® Interference Screw (ConMed Linvatec) was used for tibial fixation.

Infection cases analysis

There was an overall infection rate of 0.97 % (15 cases) after ACLR. All cases were acute infections that developed in the early post-operative period (1–5 weeks after surgery).

All 15 infections occurred in group 1 (only IV antibiotic prophylaxis without vancomycin saturation of the graft), which represents a rate of 1.85 % of infection (15 out of 810). Within this group of patients that developed an infection, a partial meniscectomy was performed in two cases and a bucket-handle tear of the medial meniscus was sutured in another patient. The bacteria isolated were as follows: 12 *Staphylococcus* species (80 %) of which 9 were CNS (60 %) and 3 *Staphylococcus aureus* (20 %); there was an infection due to *Propionibacterium acnes* and one culture-negative infection. One of the patients needed graft removal and a 2-stage ACLR procedure because of treatment failure after the third arthroscopic debridement and lavage.

There was no infection among patients who received systemic antibiotic prophylaxis and graft presoaking with vancomycin (group 2). This represented a rate of infection of 0 % (0 out of 734).

Statistical analysis showed that the prior saturation of the ACL graft in a vancomycin solution significantly reduced the infection rate ($p < 0.001$) in comparison with patients in which this technique was not performed.

Discussion

The main finding of this study was that the use of local vancomycin (presoaking of the autograft) in combination with prophylactic IV antibiotic reduced the ACLR infection rate compared with prophylactic IV antibiotics alone. The reduction in the infection rate occurred in both hamstring and BPTB groups. Based on these findings, the hypothesis was confirmed and supports the results obtained by Vertullo et al. [25].

Although knee joint infection following an ACLR is not as common as other implant-associated infections in orthopaedic surgery, the magnitude of this complication is equally important as an inadequate treatment could compromise joint function [2, 5, 23]. For this reason, different studies have been focused on the surgical management of this complication over recent years. Most of those studies concluded that aggressive arthroscopic debridement in combination with an antibiotic therapy should be the treatment of choice for this complication [1, 6, 12, 16, 21, 23]. Despite this, antibiotic treatment guidelines remain unclear.

Little has been reported about the prevention of a septic arthritis following an ACLR. Some proceedings such as antibiotic prophylaxis or limiting hair removal to the cases needing it, which are usually applied so as to avoid this complication, have been imported from other orthopaedic procedures (basically joint replacement procedures) [22, 24]. Grayson et al. [10] studied the amount of vancomycin released from the pre-soaked bovine tendons. They observed that tendons elute vancomycin into the environment in which they were placed and where they act as a reservoir of vancomycin. Furthermore, tendons with larger dimensions provide a greater reservoir. This technique was posteriorly applied in an in vivo study by them. It showed an important decrease of the rate of joint infection following an ACLR when this prophylactic measure was included in the surgical protocol [25]. Interestingly, their results were comparable to the findings observed in the present investigation.

Vancomycin is a useful bactericidal drug against staphylococci and enterococci [24] and has been described as an alternative in the treatment of *Propionibacterium acnes* implant-associated infections [18]. Vancomycin has shown to be safe for a local use [11], and it has already been used in both local prophylaxis and treatment in orthopaedics. For instance, it has been utilised with antibiotic-loaded cement spacers or nails [27], bioactive glasses or composite biomaterials [11]. Furthermore, it is a thermostable antibiotic and less toxic to eukaryotic cells than cefazolin or aminoglycosides [7]. The minimal vancomycin concentration to eradicate most of *Staphylococcus* infections is about 2 μg/ml. Grayson et al. [10] showed that this concentration can be maintained for at least 24 h when a tendon has been previously presoaked with vancomycin and this same elution was lower than the reported osteoblast and chondroblast toxicity concentrations [7].

Different studies have demonstrated that the infection rate using hamstrings autograft is higher than when using BPTB autograft [4, 15]. In the current study, the percentage of hamstring autografts used was superior in the group where the graft was presoaked. However, the infection rate was 0 % in this group. This suggests that graft presoaking with vancomycin reduces the infection rate following an ACLR despite the graft selected.

Contamination of the graft can occur during harvest or even when it is introduced into the knee through the arthroscopic portals [6]. This might explain why the infection rate in hamstring autografts is higher [15] and mostly due

to CNS (patient's skin flora around the portal). Plante et al. [17] found contamination in 23 % of hamstring autografts. Moreover, the fact that the steeping of the graft in vancomycin reduces the infection rate would give support to this theory, even though specific microbiological studies are needed to confirm this hypothesis.

Different limitations can be attributed to this study. First of all, it had a retrospective design with a lack of randomization. On the other hand, the fact that some steps in the surgical technique changed during the studied period might be considered another bias. The location of the femoral tunnel moved from an almost *over the top* position to an anatomical location in recent years, and the fixation by means of a transversal fixation has been replaced by a cortical suspensory system. This change was made because a cortical suspensory fixation system has been shown to be safer when an anatomical femoral tunnel placement is being performed [8, 9]. Regardless this variation in the fixation system in the femur, no data suggested that the decrease in the rate of infection after ACLR could be attributed to the change of fixation.

Despite these limitations, the present technique will be of relevance in daily clinical practice to prevent infection after ACLR.

Conclusions

Autograft presoaking with vancomycin in combination with classical intravenous antibiotic prophylaxis reduces the rate of knee joint infection following an ACLR in comparison with antibiotic prophylaxis alone.

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WORK 2

Knee Surg Sports Traumatol Arthrosc (2018) 26:558–562
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KNEE

Contamination occurs during ACL graft harvesting and manipulation, but it can be easily eradicated

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Abstract
Purpose Why anterior cruciate ligament (ACL) autograft soaking in a 5 mg/ml vancomycin solution decreases the rate of infection has not been well-explained. One hypothesis is that grafts can be contaminated during harvesting and vancomycin eradicates the bacteria. The purpose of the present study is to assess how the vancomycin solution acts against ACL graft contamination during graft harvesting and preparation.
Methods The study was carried out in three university hospitals over a period of 6 months. After sample size calculation, 50 patients were included in the study. Three samples were taken from each ACL graft. Sample 1 was obtained immediately after graft harvesting. After graft manipulation and preparation, the remaining tissue was divided into two parts. The raw sample was denominated sample 2 and sample 3 consisted of the rest of the remaining tissue that had been soaked in the vancomycin solution. All the cultures were incubated at 37 °C with 5% CO_2 in agar plates for 7 days (aerobically) or 14 days (anaerobically) and inspected daily for microbial growth. Any bacterial growth and the number of colony forming units were reported.
Results In seven cases (14%), either sample 1 or sample 2 was positive. In five of the cases (10%), only the sample after graft preparation was positive (sample 2). In two cases (4%), sample 1 and sample 2 were positive for the same bacteria. Isolated microorganisms corresponded to coagulase-negative staphylococci (CNS) and *Propionibacterium acnes*. No bacterial growth was observed in sample 3 ($p < 0.001$). Thus, none of those seven positive cases (0%) were positive after vancomycin soaking ($p < 0.001$).
Conclusion In the series, ACL graft harvesting and manipulation leads to bacterial contamination in 14% of the cases. This contamination is fully eradicated after soaking in the vancomycin solution in this series.
Level of evidence Level II.

Keywords ACL infection · Biofilm · Vancomycin soaking · Infection prevention · ACL contamination

Introduction

Septic knee arthritis after anterior cruciate ligament reconstruction (ACLR) has an estimated rate of approximately 1.5%, which is a slightly lower reported incidence than other orthopedic related infection [24, 28]. It has been described as the most feared and devastating complication [26]. However, a comprehensive treatment approach has shown cure rates of around 100% and better functional outcomes than other complications like ACLR-related fractures or arthrofibrosis [3, 11, 16]. To achieve it, arthroscopic debridement with graft retention along with antibiofilm antibiotics has shown optimal results in most series [13, 20, 23].

Most recently, a technique has been described to prevent ACLR infection. This measure consists of soaking the graft in a vancomycin solution. By doing so, a reduction in the infection rate to 0% in several series has been demonstrated [19, 21, 29]. With this procedure, the graft acts as

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an antibiotic reservoir eluting vancomycin over most of the microorganisms' minimal inhibitory concentration (MIC) for 24h [9]. This is the critical period when planktonic bacteria can attach itself to the implant or the avascular graft as both are recognized as foreign bodies [30].

Another supposed mechanism is that the vancomycin solution acts to kill the supposed bacteria which may contaminate the graft during harvesting [27]. Surprisingly, no previous study has focused on this theory.

The purpose of the present study is to assess how the vancomycin solution acts against ACL graft contamination during graft harvesting and preparation. The hypothesis is that the vancomycin solution reduces contamination rates during ACL graft harvesting and preparation.

Materials and methods

A prospective controlled study was performed. The study was approved by the Ethics Committee (DEXEUS-CONTBACT 6/16). All patients operated on for ACLR in three university hospitals were included. Those patients that needed an extraarticular procedure or those who received an allograft were excluded from the study. Patients with the previous knee surgeries or previous knee punctures were also excluded. The patients were operated on between June 2016 and December 2016.

During the study period, a total of 87 ACLR were initially included in the study. Thirty-seven out of these eighty-seven patients were excluded, because they did not meet the inclusion criteria. Thus, 50 patients were included for the present study and there were no further losses.

Surgical protocol

A quadrupled hamstrings' autograft or bone-patellar tendon-bone (BPTB) autograft was chosen depending on the patients' characteristics and surgeons' preferences. All operations were performed on an outpatient basis. Therefore, no drains were used after surgery. The prophylactic antibiotic protocol consisted of a single dose of 2 g of preoperative IV cefazolin or a single dose of 1 g of preoperative IV vancomycin if a type 1 penicillin allergy had been reported. As a part of the usual protocol, the ACL graft is always soaked in a vancomycin solution of 5 mg/ml. The solution was prepared by mixing 100 ml of sterile saline with 500 mg of vancomycin powder in a tray. After obtaining and preparing the graft, it was immersed in the tray, and then, it was wrapped in gauze that had been saturated with the vancomycin solution beforehand. The graft was left there for 10–15 min immediately prior to its use in the ACLR.

Source of samples

Three samples were taken from each ACL graft at three distinct points in time. The first sample (sample 1) was obtained immediately after graft harvesting. After graft preparation, the remaining tissue was divided into two parts: one of them was tagged as the second sample (sample 2) and the remaining tissue was soaked in the vancomycin solution with the graft that was to be implanted (sample 3).

A minimum sample size of 1–3 mm^3 was requested in all cases to allow further analysis.

Microbiological protocol

Each tissue was sent in separate sterile containers to the microbiological department. All cultures were incubated at 37 °C with 5% CO_2 in agar plates for 7 days (aerobically) or 14 days (anaerobically) and inspected daily for microbial growth. Any bacterial growth and the number of colony forming units were reported. Strain identification and a susceptibility test were performed using standard microbiological techniques. After study completion, each positive culture was re-evaluated by an experienced microbiologist specialized in orthopedic-related infections.

Statistical analysis

Continuous variables were presented as means (with standard deviation, SD) and ranges as percentages. Categorical data were compared between groups with the Chi-square test. A p value under 0.05 was considered statistically significant.

The Chi-square difference test was used to determine the sample size. It was assumed that there would be 17% contamination in group sample 1 and group sample 2 (as previously reported by Badran [2]) and 0% contamination in group sample 3. Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 50 subjects were necessary to recognize a difference consisting in an initial proportion of 0.17 and a final proportion of 0 as statistically significant. A drop-out rate of 5% was anticipated.

The statistical analysis was done using the SPSS Statistics 18.0 software package (SPSS Inc., Chicago, IL).

Results

There were 26 men and 24 women, and the mean age of the sample was 36.2 years (SD 11.4 years). In 29 patients, an autologous BPTP was used and 21 were treated with autologous quadrupled hamstrings. No differences in terms of

contamination were observed when hamstring and BPTB grafts were compared ($p = 0.684$). None of the patients developed septic arthritis in this series.

Contamination during harvesting and manipulation

In seven cases (14%), either sample 1 or sample 2 was positive. In five cases (10%), only the sample after graft harvest and preparation was positive (sample 2). In two cases (4%), sample 1 and sample 2 were positive for the same bacteria. Isolated microorganisms corresponded to coagulase-negative staphylococci (CNS) and *Propionibacterium acnes*. More data about those five cases can be seen in Table 1.

The effect of vancomycin soaking on contamination

No bacterial growth was observed in sample 3 ($p < 0.001$). Thus, none of those seven positive cases (0%) was positive after vancomycin soaking ($p < 0.001$).

Discussion

The results of the present study suggest that the ACL autograft is contaminated with bacteria during surgery in 14% of the cases, most often during its preparation. That contamination was completely eradicated (0%) using a 5 mg/ml vancomycin solution, thereby confirming the hypothesis.

Infections after ACLR are a potentially serious complication, but they are curable if a proper treatment is performed. For this reason, there is an increased interest in their surgical management and antibiotic treatment. The etiology has been also widely studied. Staphylococci are the most important causative agents in up to 90% of cases. Approximately half of those are due to CNS [5, 26]. Other frequently reported pathogens are *P. acnes* and occasionally enterococci, enterobacteriaceae, and *Pseudomonas* spp. [20]. *Staphylococcus lugdunensis* is considered a CNS due to the lack of production of secreted coagulase. Despite this microorganism being susceptible to most antibiotics, *S. lugdunensis* is more virulent than other coagulase-negative staphylococci and behaves like *S. aureus* in many clinical situations. Therefore, this one should be considered a virulent microorganism which can cause acute infections, including implant-associated infections [25]. It is very rarely reported as a causative agent for ACLR infections [17] as has been found in the present study where this microorganism was isolated in only one sample.

The high prevalence of CNS in acute infections is not seen in other orthopedic-related infections [30]. For this reason, some authors have related this factor to a possible contamination during harvesting and manipulation [5, 19, 20, 27]. Recently, Badran et al. have found a 17% rate of contamination during hamstring harvesting where most of the cases were due to CNS [2]. Quite the same was observed by Gavriilidis et al. They reported a 10% contamination rate [8]. Similar results have been found in the present study with a 10% rate of contamination, 60% of which were caused by CNS. Another study focused on both BPTB and hamstring grafts contamination showed similar results [10]. The only study that found a significantly higher rate of contamination is the one by Nakayama et al. in which they obtained 46% of positive samples [18]. However, this study should be carefully looked at as they used swabs for culture purposes. This technique is not recommended by experienced microbiologists [31].

Then again, it is important to understand that contamination is not equal to infection as there are factors that can kill bacteria such as preoperative antibiotic prophylaxis and the patient's own immune response. This is the reason studies on perioperative contamination during orthopedic procedures obtain higher rates than the reported clinical infection rates [1].

The relevance of ACLR infections is also shown in the studies focused on prevention. Special attention should be paid to the vancomycin soaking technique that has been recommended as a part of a protocol to reduce ACLR infection rates [14]. This simple practice that uses a solution of 5 mg/ml of vancomycin to impregnate the graft has proven to be effective in infection prevention [19,

Table 1 Details of the seven cases with positive samples

Hospital number	Age	Sex	Graft type	Sample 1	Sample 2	Sample 3
1	34	Male	BPTB	Negative	*S. epidermidis*	Negative
1	27	Female	Hamstrings	Negative	*P. acnes*	Negative
2	18	Male	BPTB	Negative	*S. epidermidis*	Negative
2	51	Male	Hamstrings	Negative	*S. Lugdunensis*	Negative
3	26	Female	BPTB	Negative	*S. epidermidis*/*S. auricularis*	Negative
1	56	Male	BPTB	*P. acnes*	*P. acnes*	Negative
1	55	Female	BPTB	*S. caprae*	*S. caprae*	Negative

21]. Similar results have been found here as none of the patients in the current series developed septic arthritis after ACLR. Although the follow-up in the present study is very short, a clear majority of ACLR infections occur in the first 4–6 weeks [27].

Vancomycin is a useful bactericidal agent against staphylococci and enterococci and has been described as an alternative in the treatment of *P. acnes* implant-associated infections [22, 30]. Vancomycin has been shown to be safe for local use, and it has already been used in both local prophylaxis and treatment in orthopedics [7]. When the graft is soaked, it acts as an antibiotic reservoir that will be eluted for hours over the MIC of the aforementioned microorganisms [9]. The other path that the soaking technique could act on to achieve a reduction in infection is by killing the contamination that occurs during graft harvesting and preparation. There is no previous report of this theory, but the present study supports the mechanism of ACLR infection reduction. Indeed, no sample was positive for any microorganism after soaking in vancomycin. Furthermore, all patients' samples in which contamination occurred were negative for bacterial growth after vancomycin soaking.

The last consideration is the comparison between the two different types of grafts employed. It has been stated that hamstring grafts have a greater risk of infection than BPTB [4, 15]. One hypothesis is that the more complex hamstrings preparation procedure and the presence of more sutures, that can act as an "extra" foreign body, will lead to more contamination [6, 12, 20]. The comparison between graft types presented here should be analyzed with caution, because it was not the purpose and due to the small sample of cases. In any case, no differences were found in the present study between BPTB and hamstring grafts in terms of contamination, similar to the results obtained by Hantes et al [10].

Some limitations can be found in the present study, the most important being the practical correlation of contamination with infection. However, the bacteria that have been identified are the same as found in clinical practice. Another limitation might be the fact that three different microbiology departments analyzed the samples. However, an experienced microbiologist specialized in orthopedic-related infections reviewed the positive samples to reduce this possible bias. The small cohort of patients could be considered another limitation, but a sample size calculation was made beforehand.

More studies should be performed to evaluate other aspects of the vancomycin soaking technique such as vancomycin joint concentrations after ACLR or its effect on supposed allograft contamination. Nevertheless, the present study provides evidential support for the use of vancomycin ACL graft soaking during ACLR in the daily clinical practice.

Conclusion

The data presented here have led to the conclusion that the harvesting and processing of ACL grafts cause bacterial contamination in 14% of all cases. This contamination is fully eradicated after soaking the grafts in the vancomycin solution.

Compliance with ethical standards

Conflict of interest We have no potential conflict of interest.

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WORK 3

Original Article 309

Infections after Anterior Cruciate Ligament Reconstruction: Which Antibiotic after Arthroscopic Debridement?

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Abstract

Arthroscopic debridement has proven to be the optimal surgical treatment for infections of the anterior cruciate ligament reconstruction (ACLR). Nevertheless, there are no reported data for the best antibiotic treatment option and its duration. The purpose of this article is to assess the usefulness of oral levofloxacin and rifampicin for the treatment of acute infections of an ACLR. This is a retrospective observational cohort study of patients operated on for ACLR over 4 years. A diagnosis of septic arthritis was based on patients' anamnesis and physical examination, laboratory parameters, and cultures of synovial fluid and/or joint tissue. Arthroscopic lavage was performed as soon as possible and tissue samples were taken. At a minimum 2-year follow-up, the infection was considered cured with a normal C-reactive protein (CRP) level and a correctly functioning and pain-free knee. Of the 810 patients, 15 (1.8%) were diagnosed as having an infection. Among the 13 staphylococcal cases (86.6%), 10 were susceptible to both quinolones and rifampicin (76.9% of the staphylococcal infections). There were two staphylococci that were rifampicin resistant. In the remaining one case, the coagulase-negative staphylococcus (CNS) was resistant to quinolones. One CNS infection was treated with linezolid and rifampicin and was the only case that needed graft removal due to treatment failure. Antibiotic treatment lasted an average of 6 weeks and oral treatment started at a mean of 5 days (range, 4–7). In the remaining 12 patients, CRP levels returned to normal at a mean of 3 weeks with good knee function and no local symptoms. Staphylococci (especially CNS) are responsible for almost 90% of acute ACLR infections in the current series. For the first time, the combination of levofloxacin and rifampicin is being proposed as a treatment in cases of an acute staphylococcal infection of an ACLR. An early switch to oral antibiotic treatment (as soon as the cultures are available) with both levofloxacin and rifampicin for a total (empiric and directed) period of 6 weeks should be considered as treatment of choice in acute staphylococcal infections of the ACLR with a retained graft. **The** level of evidence is IV (case series).

Keywords
- anterior cruciate ligament
- biofilm
- rifampicin
- knee infections
- arthroscopic debridement
- septic arthritis

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Septic arthritis following an anterior cruciate ligament reconstruction (ACLR) is a serious complication that requires a thorough comprehension of its etiology and its pathogenesis to arrive at a cure.[1]

The incidence of ACLR infection is lower than other orthopedic implant–related infections and it ranges from 0.14 to 1.8%.[2–4] Even though this represents a small number of patients, it is important to know the optimal management protocols for an ACLR infection and to be acquainted with both surgical and antibiotic treatments.

To date, it is clear that arthroscopic debridement is at least as affective as open debridement of ACLR infections.[5] More controversial is whether retention of the implant is the best option. However, recent literature shows that it is the treatment of choice when the graft is well fixed and viable.[5–7]

Reports on ACLR infection state that surgical management must always be combined with antibiotic treatment.[2,5,7–9] However, there is no study that states which antibiotics should be prescribed.

Staphylococci are the most important causative agents in up to 90% of cases. Approximately half of those are due to coagulase-negative staphylococci (CNS).[2,7–12] Other pathogens frequently reported are *Propionibacterium acnes* and occasionally enterococci, enterobacteriae, and Pseudomonas aeruginosa.[2] Therefore, the antibiotic treatment should focus on staphylococci, and those culture-negative infections could be treated as staphylococcal infections. It is obvious that it should be a wide-spectrum antibiotic and intravenously delivered in the first days and that can be switched out when cultures are available.

The main purpose of this study was to assess the usefulness of oral rifampicin and quinolones in association with arthroscopic debridement with graft retention in an ACLR infection. The duration of antibiotic treatment and the usefulness of oral treatment were also analyzed. The initial hypothesis was that, similar to other orthopedic implant–related infections, the combination of levofloxacin and rifampicin is an effective treatment for ACLR staphylococcal infections.

Materials and Methods

Study Design

A retrospective review of all the patients who consecutively underwent primary arthroscopic ACLR with an autograft in two University Hospitals was performed. Those patients who needed an extra-articular procedure or those who received an allograft were not included in the study. Patients were operated on between January 2006 and December 2009.

All patients were operated on by the same surgical team composed of four senior surgeons. All operations were performed on an outpatient basis. The prophylactic antibiotic protocol consisted of a single dose of 2 g of preoperative intravenous (IV) cefazolin. If a penicillin allergy was reported, a single dose of 1 g of preoperative IV vancomycin was administered.[13] No patient in this series informed of having an allergy to vancomycin. The types of graft employed were a quadrupled hamstrings and a bone–patellar tendon–bone (BPTB). No drains were left after surgery.

Diagnostic Criteria for Septic Arthritis

Diagnosis of septic arthritis was based on patients' anamnesis, physical examination, laboratory parameters, and cultures of synovial fluid and/or joint tissue. Synovial aspiration was performed as soon as the diagnosis was suspected. The liquid obtained was immediately sent for biochemical analysis and cell count analysis in heparin tubes. The remaining synovial fluid was introduced into aerobic and anaerobic blood culture bottles for automatic colorimetric bacterial detection (BacT/ALERT Culture Media, BioMérieux, Marcy-l'Étoile, France). These bottles contain activated charcoal to neutralize antimicrobials and make for a more accurate diagnosis.[14]

Surgical Approach

When an ACLR infection was confirmed or highly suspected, an arthroscopic lavage was performed as soon as possible and tissue samples were taken. ACL graft indemnity was evaluated. It was not removed when it was considered viable and well fixed. An empiric IV antibiotic regimen (vancomycin plus ceftazidime) was started until the cultures results were available.

Criteria for Infection Healing

At a minimum 2-year follow-up, the infection was considered cured with a normal C-reactive protein (CRP) level and a correctly functioning and pain-free knee. Functional outcome measures were previously reported and do not constitute the core of the current work.[7] The functional assessment included a detailed physical examination (including the pivot-shift and Lachman tests), an arthrometric evaluation with KT-1000 (MEDmetric, San Diego, CA), functional scores (modified Lysholm and Gillquist scoring scale), the International Knee Documentation Committee (IKDC) form), and radiographic evaluation (standard anteroposterior and lateral views as well as Rosenberg view). In the radiological evaluation, osteophyte formation and either medial or lateral joint space narrowing were assessed.

Statistical Analysis

Continuous variables are expressed as mean and standard deviations (or range) and categorical variables were presented as means and percentages. When two related items of data were analyzed, the chi-square or Fisher exact test was used. In all cases, a p-value of less than 0.05 was considered statistically significant. The statistical analysis was done using the SPSS 18.0 (SPSS Inc., Chicago, IL) statistical package.

Results

There were 810 patients who underwent ACLR during the inclusion period; 112 were women (13.8%) and mean age was 33.5 years (SD, 7.6). There were 15 ACLR infections (1.8%). The statistical analysis did not show any difference between the infection group and the rest of the sample in terms of age, sex, and body mass index ($p > 0.05$).

All of the cases were acute infections that occurred in the early postoperative period. The isolated bacteria were as

Table 1 Anterior Cruciate Ligament (ACL) infection treatment

Case	ACL graft	Microorganism	Antibiotic	CRP at end follow-up	Number of arthroscopic lavages	Antibiotic therapy duration (wk)
1	Hamstring	*S. aureus*	Levofloxacin + rifampicin	0.4	1	8
2	Hamstring	MRSA	Levofloxacin + rifampicin	0.6	2	6
3	Patellar tendon	*P. acnes*	Amoxicillin + clavulanic acid	0.5	1	6
4[a]	Hamstring	CNS	Linezolid + rifampicin	0.2	3	6
5	Hamstring	CNS	Levofloxacin + rifampicin	0.2	1	6
6	Patellar tendon	CNS	Trimethoprim/sulfamethoxazole+ rifampicin	0.2	2	6
7	Hamstring	CNS	Levofloxacin + rifampicin	0.2	2	5
8	Hamstring	CNS	Ciprofloxacin + rifampicin	0.9	1	6
9	Hamstring	*S. aureus*	Ciprofloxacin	0.9	1	4
10	Hamstring	Unknown	Amoxicillin + clavulanic acid	0.2	1	6
11	Hamstring	CNS	Levofloxacin + rifampicin	0.6	1	6
12	Hamstring	CNS	Levofloxacin + rifampicin	0.5	1	6
13	Hamstring	CNS	Levofloxacin + rifampicin	0.2	1	6
14	Hamstring	CNS	Levofloxacin	0.2	1	6
15	Hamstring	CNS	Levofloxacin + rifampicin	0.3	1	6

Abbreviations: CNS, coagulase-negative staphylococcus; CRP, C-reactive protein (mg/dL); MRSA, methicillin-resistant *S. aureus*.
[a]Patient who required graft removal.

follows (►**Table 1**): 13 *Staphylococcus* species (86.6%) of which 10 (66.6%) were CNS and 3 *Staphylococcus aureus* (20%); there was 1 infection due to *P. acnes* and 1 culture-negative infection. Among the 13 staphylococcal cases (86.6%), 10 were susceptible to both quinolones and rifampicin (76.9% of the staphylococcal infections). In two cases, the microorganisms were rifampicin resistant. In the one remaining case, the CNS was resistant to quinolones. Alternative antibiotic treatment in those resistant cases can be seen in ►**Table 1**. It is of remarkable interest that one of the quinolones- and rifampicin-susceptible CNS was treated with linezolid and rifampicin. This was the only case in which the graft had to be removed and needed a two-stage ACLR procedure due to the treatment failure after the third arthroscopic debridement and lavage (persisting pain and purulent drainage). One of the staphylococcal cases was due to methicillin-resistant *S. aureus*. Even in this case, the antibiotics of choice were levofloxacin and rifampicin with good outcome.

Antibiotic treatment lasted a median of 6 weeks (empirical treatment intravenously delivered plus orally directed therapy). Oral treatment started as soon as culture results were available. No side effects were reported in patients treated with quinolones and rifampicin.

In all but one patient (the one who needed graft removal), CRP levels returned to normal at a mean of 3 weeks without local symptoms. Function and pain improved, although these patients never reached functional scores like those patients without infection.[7]

Discussion

The results presented in this study suggest that the combination of oral levofloxacin and rifampicin is an effective treatment for ACLR infections after arthroscopic debridement when the graft is retained. Therefore, the hypothesis is confirmed. The second finding is that a total antibiotic treatment period of 6 weeks is enough for these types of implant infections.

Although knee joint infection following an ACLR is not as common as other implant-associated infections in orthopedic surgery, the magnitude of this complication is equally important as an inadequate treatment could compromise joint function.[7] For this reason, different studies have focused on the surgical management of this complication over recent years. Most of those studies concluded that aggressive arthroscopic debridement in combination with an antibiotic therapy should be the treatment of choice for this complication.[2,4,6–8,15] The issue that has recently sparked interest is the prevention of ACLR infection that has led to the development of several techniques. One is graft soaking in vancomycin, which has been demonstrated to be effective.[16,17] Despite this, antibiotic treatment guidelines remain unclear.

Reports in the literature on ACLR infections manifest that after surgical treatment, antibiotic treatment should be prescribed with the advice of the infectious diseases specialist, taking into account the culture results and the susceptibility of the microorganism. However, with that statement, several schedule treatments are usually available and it is not clear whether one might be superior to the other.

Several guidelines have been published for the treatment of prosthetic joint infections.[18–20] It is well known that the key to implant-related infections is the biofilm treatment.[24] For that purpose, those guidelines based on either clinical trials or animal model studies recommend the use of rifampicin in combination with another antibiotic for the treatment of staphylococcal infections.[21–23] For the susceptible staphylococci, quinolones are a combination that has shown proven efficacy,[21] even with oral administration. This might be explained as both quinolones and rifampicin are bactericide and penetrate well into bone tissue and joints.[13] Based on the aforementioned studies, the patients presented in this study have been treated with the same protocol with good outcomes and infection curing. The duration of the treatment has been modified and reduced to 6 weeks (half the recommended time for a prosthetic joint infection[19,20]) and the ACLR infection was cured in all patients that followed a quinolone–rifampicin treatment. One explanation for this success with a shorter treatment period might be the minor amount of biofilm due to a smaller device compared with a prosthesis. Then, ACLR infections operate like an entity somewhere between native septic arthritis of the knee and a knee arthroplasty infection.

An early oral switch (as soon as cultures are available) to levofloxacin and rifampicin is an effective and safe treatment for ACLR infections. The advantage is that these drugs can be administered orally and would permit early patient discharge.

One concern in the present study is the treatment failure of the only patient that received linezolid in combination with rifampicin. Of course, it is only one case but there are in vitro studies that show the superiority of the combination of levofloxacin and rifampicin over linezolid and rifampicin.[24]

An interesting point of the present study is the high prevalence of CNS infections. Some authors have related the origin of these infections to graft contamination during harvesting or even when it is introduced into the knee through the arthroscopic portals.[2] This might explain why the infection rate in hamstring autografts is higher than with BPTB autografts and is mostly due to CNS (patient's skin flora around the portal). However, specific microbiological studies are needed to confirm this hypothesis.

Different limitations can be attributed to this study. First of all, the retrospective design of the study and the lack of a control group make it difficult to know whether other treatments would be as effective. Then, there is the small number of patients, even though it is the largest series described in the literature, to the best of our knowledge.

Conclusion

Oral antibiotic treatment with levofloxacin and rifampicin for a period of 6 weeks should be considered as the treatment of choice in acute staphylococcal ACLR infections with a retained graft after arthroscopic debridement.

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Literature Review on ACL-R

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REVIEW ARTICLE

Managing septic arthritis after knee ligament reconstruction

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Abstract
Purpose Joint infection after anterior cruciate ligament (ACL) reconstruction is uncommon but has potentially serious consequences for the graft and articular cartilage. Most recently published series are in agreement that an urgent arthroscopic washout and antibiotic treatment are mandatory to preserve both graft and cartilage. However, several questions have not as yet been touched upon.
Methods We performed a literature review to assess the most interesting series published about this issue.
Results In this review, a management protocol is first presented that discusses the different diagnostic parameters to consider and surgical and antibiotic treatment suggested according to the literature. Outcomes published in different series are also discussed.

Keywords Anterior cruciate ligament · ACL · Infection · Septic arthritis · Joint infection · Knee · Debridement · Antibiotic

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Introduction

The number of anterior cruciate ligament reconstructions (ACLR) performed over recent years has increased and is expected to increase further in coming years. Knee-joint infection following this procedure is an uncommon but serious complication. Therefore, it is important to understand the natural history of this complication and its devastating consequences if not swiftly acted upon. Depending on the time elapsed since apparition to diagnosis of infection and establishment of correct therapy, the infection may have no consequences for the joint or it might imply a loss of the ACL graft viability, injury to the articular cartilage or even early osteoarthritis. In 1998, Matava et al. [1] performed an interesting study in which a questionnaire was directed to different orthopaedic fellowship programme directors that asked about the best way to manage an infected knee after an ACLR. That study highlighted the lack of conclusive evidence, making it difficult to arrive at a consensus with regard to the best way of managing it. In this review, prevalence, aetiopathology, diagnosis, the most accepted treatment method and functional outcomes after this complication are described.

Prevalence

Several series showing different rates of knee-joint infection following ACLR have been published over recent years. The lowest rate was presented by Indelli et al. [2], who reported a rate of 0.14 % for septic arthritis in a series of 3500 consecutive ACLR patients. On the other hand, the highest published rates are by Torres-Claramunt et al. [3] (1.8 % in a series with 810 consecutive ACLR) and Shollin-Borg et al. [4] (1.7 % in a series with 575 ACLR). Viola et al. [5] reported a retrospective series with 13 patients diagnosed with septic arthritis

following ACLR performed with a bone–patellar tendon–bone (BPTB) autograft. Eleven of 13 of these infections were observed in 70 consecutive ACLRs, and the other two infections were reported amongst 1300 ACLRs. It was possible to identify a contamination source in an inflow cannula in which coagulase-negative *Staphylococcus* (CNS) was seen. When this source of contamination was eradicated, the infection rate decreased dramatically. Sechriest et al. [6] observed a similar situation in their study. They identified a yearly ACLR infection incidence of 4.4 %, which obliged them to temporarily suspend all ACLR procedures. They ultimately observed different shortfalls in the surgical equipment decontamination and sterilisation process that ultimately led to the development of an infection-preventing pathway for patients and providers. Sonnery-Cottet et al. [7] also presented a consecutive series with 1957 ACLRs with an infection rate of 0.61 %. Those authors observed that this rate increased to 5.7 % in a subgroup of professional athletes that included 88 patients. The remaining patients (1869), considered non-professional athletes, had an infection rate of 0.37 %. As 23 % of the professional athlete group had a combined ACLR and lateral tenodesis, the authors concluded that being professional athletes and having an associated lateral tenodesis when an ACLR was performed were risk factors for the development of infection. Judd et al. [8] published a series with 1615 consecutive ACLRs performed over seven consecutive years in which 11 (0.68 %) cases of postoperative knee-joint infections were observed. Those 11 infections occurred in a subgroup of 418 consecutive ACLRs performed over three consecutive years. There were no infections in the remaining four year period (1197 ACLRs). Although the grafts used in these 418 ACLRs were similar, using either a BPTB or a hamstring autograft, all infections occurred with hamstring autografts. Those authors also observed a higher incidence of infection in patients with prior knee surgery [relative risk (RR) 1.9].

In summary, although most series have shown rates of infections <1 % following an ACLR, some series (or different subgroups within those series) reached rates >1.5 %. Moreover, an open surgical procedure associated with ACLR or previous knee surgery might lead to an increase in these rates of infection.

Aetiopathology

Fong and Tan [9] presented a series with 472 cases of consecutive ACLR in which they observed seven cases of postoperative joint infection. These seven cases were classified with regard to time elapsed from surgical procedure. Patients were classified as acute (<2 weeks), subacute (2 weeks to 2 months) and late (>2 months) infection; none of these infections was classified as late infection. While this classification uses an appropriate two week cutoff point to differentiate between acute and subacute infections, eight weeks might be excessively long to differentiate between subacute and late infection, considering infection aetiology. In fact, knee-joint infections occurring four or five weeks after ACLR may be considered late. Source of infection and the moment at which microorganisms invaded the joint have not been clearly defined [8–13].

S. aureus and CNS (*S. epidermidis* and other coagulase-negative species) are the most common bacteria found in most series [2, 3, 5, 7, 10, 11, 14–16]. Additionally, different methicillin-resistant *S. aureus* or anaerobium microorganisms have also been cultured as the origin of such infections. This fact should be considered when empirical antibiotic treatment is initiated [3, 14]. *Staphylococcus* is a microorganism capable of forming a biofilm within the first few weeks that protects itself from antimicrobials, thus making it difficult to eradicate [17]. It is therefore important to initiate treatment as early as possible to preserve both graft and cartilage [18].

Infection rate following ACLR differs depending on the graft used [8, 14, 19, 20]. Recently, Brophy et al. [21] reported that a patient with diabetes who receives a hamstring auto- or allograft has an increased risk of infection following ACLR. Additional surgical procedures during ACLR are also considered a risk factor [7, 11, 19]. This might not only be due to the need to add an open surgical approach but also due to increased surgical time. Finally, prior surgical procedures in the same knee [4, 8, 22], the use of drains and of different types of graft fixation [8, 23] are considered risk factors for septic arthritis following ACLR.

With regard to new prophylactic measures described to decrease infection rate following ACLR, recent investigations demonstrated that presoaking the autograft in a diluted solution of vancomycin is effective for this purpose [24–26]. Other measures, such as the use of gentamicin irrigation solution, have been shown as less effective [27].

Diagnosis

Joint aspirate is the main diagnostic test to confirm an infection and is mandatory before starting antimicrobial treatment. In fact, infection is undoubtedly confirmed when a positive culture is obtained from aspirate or when synovial cell count is consistent with this diagnosis [28]. Paci et al. [29] studied postoperative synovial fluid in patients who had undergone ACLR and observed that granulocyte values >16,200 g/mm^3 might be considered a good cutoff point to define this fluid as infected, with a susceptibity of 86 % and a specificity of 92 %. The susceptibity of synovial fluid culture is slightly >80 %. However, Gram-stain susceptibity is <50 %. Thus, a negative result does not preclude the diagnosis of septic arthritis. In most series, most microorganisms were identified [3, 4, 7–9, 11, 13, 14, 30]. However, some series report only 14 % of microorganisms as being identified [14]. On the other hand, it

is important to emphasise that the evolution of testing for C-reactive protein (CRP) and erythrocite sedimentation rate (ESR) values in the postoperative period after ACLR can be helpful to diagnose and monitor an infection [31–34].

To summarised, when septic arthritis after ACLR is suspected, a blood test and synovial fluid aspiration are absolutely mandatory. If the biochemical fluid analysis or the Gram stain is conclusive, it can be diagnosed as septic arthritis. If these values are not conclusive but CRP value and white blood cell count (along with high clinical suspicion) are suggestive of knee-joint infection, the problem should be treated as septic arthritis at least. Due to the deleterious effects of joint infection, treatment must be initiated with haste. In the list below, we suggest a diagnostic protocol to define septic arthritis following an ACLR; one diagnostic parameter or at least two highly suspicious parameters are diagnostic of septic arthritis after ACLR.

1. Diagnostic
   - Positive culture or positive Gram
   - Purulent aspect of the aspirate
   - Polymorphonuclear cell percentage >90 %
   - Cell count >100,000
2. Highly suspicious
   - Turbid aspect
   - Polymorphonuclear cell percentage; from 75 % to 90 %
   - Cell count; from 20,000 to 100,000
   - Glucose: <50 % serum level
   - CRP value; >150 mg/dl day 3, or >20 mg/dl day 15

Treatment

Protecting the articular cartilage and the ACL graft are the two main objectives of treatment. With new knowledge gained over recent years and the lack of standard guideliness for treatment, here we present a new algorithm of treatment for this complication (Fig. 1). Recently, Abdel-Aziz et al. [39] proposed a similar algorithm, which they used in a large series of 2560 ACLRs. They treated 24 cases of infection with this algorithm, obtaining good results. Different authors have used isolated non-operative treatments. Viola et al. [5] chose antibiotic treatment with ciprofloxacin plus amoxicillin/clavulanic acid for a period of 15–90 days; in >40 % of cases, treatment failed, and patients required an arthroscopic lavage. Monaco et al. [40] described antibiotic therapy along with repeated joint irrigation; that treatment failed in 30 % of patients and required an arthroscopic lavage. Contrary to those results, Wang et al. [16] presented a series with 21 cases of infection following an ACLR, some of which were treated conservatively. As the study authors acknowledged, this treatment was chosed because they were short of experience in their early cases. Both treatments, non-operative and operative, were reported as being effective. In the non-operative group, fever decreased at a mean of 9.2 days and antibiotic therapy IV was 27.7 days. In the

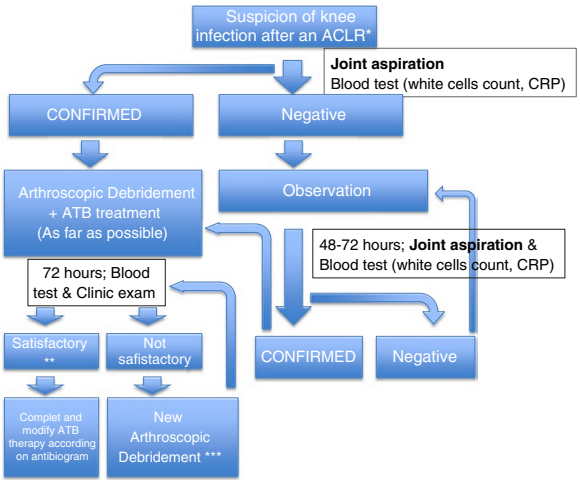

Fig. 1 Management algorithm for knee-joint infection following anterior cruciate ligament repair (ACLR). **Satisfactory is defined as a decrease in C-reactive protein (CRP) values and improvement in clinical signs of infection. *** In cases in which three arthroscopic lavages are necessary to resolve infection, we recommend removing the graft and hardware if a fourth washout is needed. Table 1 shows the different diagnoses and subsequent treatments performed by different authors.

Table 1 Literature review

Study	Year of publication	No. knees	Incidence [*n* (%)]	Graft	Most common pathogens[b]	Days until diagnosis	Empiric antibiotic	Weeks IV/ oral (total)[a]	Mean number lavages	Grafts removed
Burks et al. [14]	2003	1918	8 (0,42 %)	7 HT 1 BPTB	3 SA 1 PA	19	Not reported	6/0 (6)	2	7
Barker et al. [35]	2010	3126	18 (0.58 %)	5 HT 7 BPTB 6 Allo	6 SA 4 CNS 2 *P. acnes* 6 Unknown	32	Not reported	(6)	1.38	5
Fong and Tan [9]	2004	472	7 (1 %)	7 HT	4 SA 3*Pepto* 1 *Klebsiella* 1 *Enterobacter*	24.5	Not reported	2.5/4 (6.5)	1.4	0
Indelli et al. [2]	2002	3500	6 (0.14 %)	4 BPTB 2 Allo	3 SA 2 CNS 1 *Strep*	33.5	Not reported	6/6 (6)	2.3	2
Judd et al. [8]	2006	1615	11 (0.68 %)	11 HT	1 SA 8 CNS 1 *Enterobacter* 1 *Propioni*	14.2	Cefazolin/ vancomycin	4/4 (4)	2.4	1
Katz et al. [36]	2008	801	6 (0.75 %)	2 HT 4 Allo	1 SA 6 CNS 1 *P. acnes*	16.4	Not reported	4–6 weeks	–	5
Shollin-Borg et al. [4]	2003	575	10 (1.7 %)	4 HT 6 BPTB	1 SA 6 CNS 1 *Propioni* 2 Unknown	15.4	Not reported	4–12 weeks	1 (and continuous irrigation)	0
Van Tongel et al. [30]	2007	1736	15 (0.86 %)	12 HT 2 BPTB 1 Allo	1 SA 8 CNS 1 *Enterococcus* 1 *E. cloacae* 3 Poly	10.9	Cloxacillin/ gentemycin	4/10 (±14)	1.9	1
Viola et al. [5]	2000	1794	13 (0.78 %)		2 CNS	7.7	Ciprofloxacin/ amoxicillin plus clavulanate	15–90 days	0.46	0
Shulz et al. [13]	2007	3077	24 (0.78 %)	12 BPTB 7 HT 4 Vicryl band 1 Trevira band	12 SA 5 CNS 2 *Strep* 4 Unknown	61.7	Ampiciline/ Sulbactam	Not reported	3.95	17
Schub et al. [37]	2009	4068	21 (0.52 %)	20 HT 1 Allo	3 SA 12 CNS 1 *E. faecalis* 1 *Coryne*	16.4	Vancomycin or cephalosporin	3/3 (3)	0.7	0
William et al. [19]	1997	2500	7 (0.3 %)	3 HT 4 BPTB	6 SA 2 CNS 1 *Pepto*	21.8	Ceftazidime/ vancomycin	4–6/- (4–6)	1.57	4
Sonnery-Cottet et al. [7]	2011	1956	12 (0.61 %)	7 HT 4 BPTB 1 QT	11 CNS 1 *Propioni*	15.6	Not reported	Not reported	1.25	0
Torres-Claramunt et al. [3]	2013	810	15 (1.8 %)	11 HT 4 BPTB	3 SA 10 CNS 1 *Propioni*	23.9	Ceftazidime/ vancomycin	2–3/3 (6)	1.3	1
McAllister et al. [11]	1999	831	4 (0.48 %)	1 HT 3 BPTB	4 SA	11.2	Not reported	4.7/3 (7.7)	2.75	0
Binnet et al. [20]	2007	1231	6 (0.49 %)	4 BPTB 2 HT	3 SA 1 PA	22	Cefazolin	3/- (3)	2.66	0
Sajovic et al. [38]	2009	1283	3 (0.23 %)	3 HT	1 SA 1 CNS 1 Unknown	8	Cloxacillin	2/4 (6)	1	0

Table 1 (continued)

Study	Year of publication	No. knees	Incidence [*n* (%)]	Graft	Most common pathogens[b]	Days until diagnosis	Empiric antibiotic	Weeks IV/ oral (total)[a]	Mean number lavages	Grafts removed
Abdel-Aziz et al. [39]	2014	2560	24 (0.93 %)	24 HT	7 CNS 7 SA 1 *E. faecalis* 1 *E. coli* 2 *Propioni* 1 *Strep* 2 *Pepto* 3 Unknown	12	Cephalosporin or vancomycin EV	4/- (–)	3	3

[a] The total duration of the antibiotic treatment is not well-documented in all studies. Total duration is the summation of IV and oral treatment, although in some cases, it is simply referred to as IV treatment duration

HT hamstring, *BPTB* bone–patellar tendon–bone, *allo* allogenic, *SA Staphylococcus aureus*, *CNS* coagulase-negative staphylococcus, *Propion Propionebacterium*, *Strep Streptococcus*, *PA Pseudomonas aeruginosa*, *Coryne Corynebacterium*, *E. faecalis Enterococcus faecalis*, *E. cloacae Enterococcus cloacae*, *Pepto Peptostreptococcus*, *Poly* polymicrobial

operative group, fever lasted for 1.5 days, and antibiotic therapy IV was stopped after 19 days.

Overall, it is accepted that the treatment of choice is arthroscopic lavage, performed as soon as possible, along with beginning antibiotic treatment IV in most published series [10, 41]. During arthroscopic debridement, it is mandatory to gather samples for culturing before antibiotic administration, and both therapies must be performed as soon as possible. Even if the diagnosis is not completely confirmed, it is always preferable to perform the arthroscopic washout prior to beginning antibiotic treatment; however, if the surgical procedure cannot be performed immediately, antibiotic therapy must still be initiated. Arthroscopy must include extensive lavage with normal serum, debridement of devitalised tissue, removal of fibrin clots and synovectomy. It is also suggested to remove the fibrin layer covering the graft surface [3] and evaluate the macroscopic integrity of the graft as well as its tension. If the graft is not viable, it should be removed, along with fixation hardware. Antibiotic therapy should be initiated immediately after culture samples are taken. A new blood test should be done at 72 hours. If clinical and/or laboratory parameters are not satisfactory (e.g. improving from pre-operative values), a new arthroscopic washout must be performed.

Although most series recommend specific antibiotic treatment in accordance with micro-organism susceptibity, most failed to report whether empirical antibiotic therapy IV was previously initiated. Some authors reported that all patients were empirically treated with cephalosporin or vancomycin when the infection was first diagnosed [8, 16]. Van Tongel et al. [30] preferred to use a combination of cloxacillin and gentamycin. However, in many cases, bacteria were resistant to the empiric antibiotic treatment, and antibiotics must be changed when culture sensitivities are obtained; other series did not mention whether they used empiric antibiotic treatment. Empiric antibiotic treatment should be effective against most microorganisms described for this infection—not only against the *Staphylococcus* group, including CNS and methicillin-resistant subgroups, but also against Gram-negative microorganisms, as this infection is comparable with a prosthetic joint infection [42]. In our series [3], vancomycin (1 g/12 h) and ceftazidime (2 g/8 h) were initiated after obtaining joint aspirate or after the arthroscopic procedure. We propose this combination as empirical antibiotic therapy for this type of complication.

There is also controversy regarding how long the antibiotic should be administered and when to switch from IV to enteral administration. Although the duration of antibiotic treatment can vary between four [36] and 14 [30] weeks, most authors agree that it should be provided for not less than six weeks. There is also consensus that IV administration is preferable for the first two to three weeks [3, 9, 16]. However, the precise duration of IV treatment should be determined based on the microorganism cultured, its susceptibities and postoperative clinical and laboratory parameters [43]. Thus, the final antibiotic regimen must consider a number of factors.

Post-operative physical therapy is not described in all series. In most series, however, continuous passive motion was initiated in days following debridement, and weight bearing was not initially allowed. While in some series weight bearing was allowed when wounds were clinically healed [19], other series waited until the sixth post-operative week [11, 37]. Our recommendation is to initiate in the firsts post-operative days a graded knee-strengthening programme including quadriceps and hamstrings strength through progressive isometric, isotonic and isokinetic exercises. Moreover, range of motion (ROM) might be progressively increased. All these exercises might be initiated when symptoms suggestive of infection disappear. In our point of view, progressive weight bearing could be also allowed at this time, achieving complete weight bearing by the sixth post-operative week [3]. Figure 1 summarises the management algorithm suggested by us.

Functional outcomes

A satisfactory result after treatment of an infected ACLR should be defined as good functional scores, preserved articular cartilage architecture, preserved ACL graft, restored full ROM or return to previous level of activity. However, previous series provided only some of these aspects. In addition, most series only reported very short follow-up results [8, 9, 14]. Different authors considered a mean Lysholm score of 65.6 [13] or 69.5 [40] to be satisfactory. More in accordance with current standards of satisfactory results, Lysholm score >90 points [5, 14, 15, 41] has also been reported. In our series [3], a mean Lysholm score of 77.7 and a mean International Knee Documentation Committee (IKDC) score of 70.4 at a mean follow-up of 39.3 months were achieved. Conversely, the control group had a mean Lysholm score of 90.7 and a mean IKDC of 86.6. Surprisingly enough, Monaco et al. [40] reported on a series of patients who were able to return to preoperative sports at the same level. Shulz et al. [13] reported a 60-day mean time to diagnose the infection, and in one case, a total joint arthroplasty had to be performed five years after ACLR. They concluded that subjective and clinical results after this complication were clearly inferior to those of "unproblematic" ACLR. Boström Windhamre et al. [44] studied functional outcomes in 27 patients after infected ACLRs with 60 months of follow-up, indicating no inferior objective knee function or lower degree of patient satisfaction. However, patients required a longer rehabilitation period, and fewer patients returned to sports. Gille et al. [45] reviewed 31 patients with infection after ACLR from 1993 to 2010; of these 31 patients it was possible to maintain the graft in eight only. They confirmed that patients that had not been diagnosed early presented worst results than those arthroscopically managed in the immediate postoperative period.

With regard to the KT-1000 arthrometer test, we obtained a mean difference of 1.3 mm when the injured knee was compared with the non-injured knee [3]. In fact, in four of 15 patients, this difference was ≤1 mm. Monaco et al. [40], in a series with 14 infections, observed a mean KT-1000 side-to-side difference of 2.5 mm (follow-up, 38 months) and Binnet et al. [20] observed that this value was 2.7 mm (follow-up, 102 months). It seems that, if the graft can be maintained, the laxity obtained in most cases is similar to those patients who have not had an infection. A combination of glycosaminoglycan and collagen depletion after a joint infection, along with some degree of arthrofibrosis, might help explain these results [46].

Shub et al. [37] published a study with four cases of infections following ACLR with a mean follow-up of 17.9 years and reported that patients had diminished subjective, functional and radiographic outcomes compared with uncomplicated cases. Compared with an earlier functional follow-up, those patients improved in terms of pain and remained stable in terms of both functional scoring and activity-related subjective scales. Although radiographic studies revealed arthritis progression in all patients and a torn graft in one, no patient required additional surgery at almost 18 years after the infection.

While hamstring autografts are more susceptible to infection, patients with an ACL reconstructed with a BPTB autograft have 2.75 more possibilities of presenting degenerative changes after a knee infection [11, 30]. Scholling-Borg et al. [4] also showed a worse Knee Injury and Osteoarthritis Outcome Score (KOOS) in patients with infection after ACLR with a BPTB autograft than those with a hamstring autograft. However, other independents factors might also contribute to degenerative changes. *S. aureus* infection, two or more debridements and allografts have also been related with these finding [43].

Summary

Following is a summary of findings from our literature review:

- The rate of joint infection after an ACLR is <to 1 % in most series.
- Concomitant open surgery or previous surgery on the same knee increases the risk of septic arthritis following ACLR.
- Most of these infections are caused by *Staphylococcus*, mainly CNS, and it seems that the infections are introduced during the surgical procedure.
- In most series, infection occurs during the first postoperative month. Close patient monitoring and a high index of diligence are needed for a proper and early diagnosis.
- The most used classification groups such infections into: acute (<2 weeks), subacute (2 weeks–2 months) or late (>2 months). We believe this classification can be improved. However, the two month cutoff point for differentiating between subacute and late infection seems unreasonably long. Instead, four weeks might be a more appropriate cutoff time.
- Presoaking the graft with a vancomycin solution seems a good option for lowering infection rates.
- Joint aspiration and a blood test are essential for diagnosing infection. However, if the infection cannot be formerly diagnosed but analytical parameters and a high clinical suspicion suggest it, it should be treated as a knee-joint infection.
- Treatment must be initiated as early as possible. A combination of arthroscopic debridement and antibiotic therapy are the basis of this treatment. Antibiotic treatment initiated empirically may be agreed upon with the

infectious diseases department, but this initial treatment should be similar to that used in a prosthetic infection.
- If clinical and laboratory parameters do not improve within 48–72 hours, a new arthroscopic lavage should be considered. If the graft is viable, it may be possible to retain it.
- Intravenously administered antibiotic treatment should be maintained until clinical and analytical parameters normalise. Overall, antibiotic treatment is maintained for a minimum of six weeks.
- Function after septic arthritis following ACLR is impaired. While good functional outcomes can be achieved, full return to athletic activities cannot be always acomplished.

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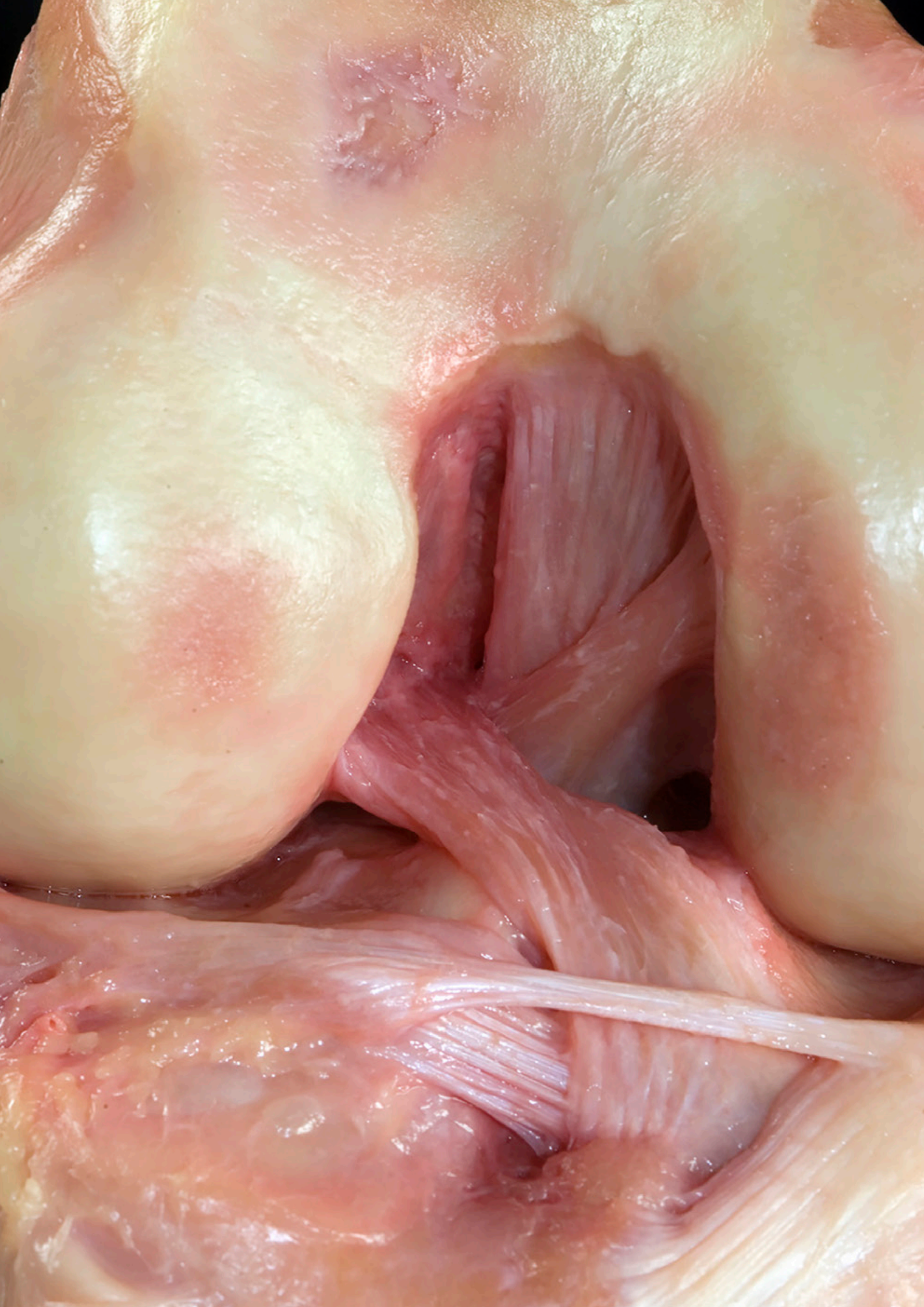

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