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PII: S0163-4453(23)00193-7

DOI: https://doi.org/10.1016/j.jinf.2023.03.021

Reference: YJINF5927

To appear in: *Journal of Infection*
Accepted date: 28 March 2023

Please cite this article as: Nora Renz, Tomislav Madjarevic, Matteo Ferrari, Roland Becker, Christen Ravn, Charles Vogely and Daniel Pérez-Prieto, Recommendations on diagnosis and antimicrobial treatment of infections after anterior cruciate ligament reconstruction (ACL-R) endorsed by ESSKA and EBJISRunning title: Management of infections after anterior cruciate ligament reconstruction (ACL-R), *Journal of Infection,* (2023) doi:https://doi.org/10.1016/j.jinf.2023.03.021

Recommendations on diagnosis and antimicrobial treatment of infections after anterior cruciate ligament reconstruction (ACL-R) endorsed by ESSKA and EBJIS

Running title: Management of infections after anterior cruciate ligament reconstruction (ACL-R)

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Declaration of interest:

none

SUMMARY

Infection after anterior-cruciate ligament reconstruction (ACL-R) is a rare but devastating complication affecting predominantly young and sportive individuals. A timely and correct diagnosis as well as an optimized management are paramount to circumvent serious sequelae and compromise in life quality. These recommendations are primarily intended for use by infectious disease specialists

and microbiologists, but also orthopedic surgeons and other healthcare professionals who care for patients with infections after ACL-R. They are based on evidence mainly originating from observational studies and opinions of experts in the field and cover the management of infections after ACL-R with a special focus on etiology, diagnosis, antimicrobial treatment and prevention. Comprehensive recommendations on prevention, surgical treatment and rehabilitation are presented separately in a document primarily addressing orthopedics professionals.

KEYWORDS

anterior cruciate ligament reconstruction; diagnosis; leukocyte count; septic arthritis; implant

BACKGROUND

The number of anterior cruciate ligament reconstructions (ACL-R) has increased in the last years and is estimated to rise further in future[1]. The prevalence of infection after ACL-R has been described to be low in several analyses, with professional athletes being at higher risk than nonprofessional individuals (5.7% vs. 0.37%, respectively)[2]. It represents a serious complication entailing devastating sequelae in case of delayed diagnosis and non-optimized therapy. The population of patients at risk is mainly of young age and highly demanding aiming for rapid recovery and return to sport[2]. Solid data on optimized diagnostic and therapeutic measures is scarce, however there is a fourfold increase in articles published on PubMed during the last decade, underlining the increasing interest in the clinical and scientific community dealing with these infections.

The European Bone and Joint Society (EBJIS) proposed a literature review and a work-group on septic arthritis in native joints to give recommendations on diagnosis and treatment. The section of ACL-R infections was joined by the European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) to provide a conjoint list of recommendations. Therefore, here are delivered recommendations for the diagnosis and management of infections after ACL-R, based an international board of orthopedic surgeons and infectious diseases specialists. Part of these recommendations was published previously embedded in the guideline for management of septic arthritis in native joints (SANJO)[3].

The aim of this literature review is to give practical guidance for healthcare professionals involved in the management of patients suffering from infections after ACL-R. The work covers epidemiology, risk factors, clinical and microbiological spectrum, diagnosis, antimicrobial therapy and prevention of infections after ACL-R.

Due to the low incidence of this complication after ACL-R and the resulting paucity of published high-quality studies evaluating respective diagnostic and therapeutic approaches, many recommendations or suggestions are extrapolated from other joint-related infections such as septic arthritis or

periprosthetic joint infections (PJI), for which more high-quality studies have been performed. We therefore refrain from specifying any strength of recommendation or quality of evidence. The statements are based on the literature, mainly observational studies, and on the clinical experience of the orthopedic surgeons and infectious diseases specialists involved.

MICROBIOLGY AND PATHOGENESIS

1. What are the most common pathogens that cause infection after ACL-R?

The most common pathogens isolated in infections after ACL-R are staphylococci (60-90%), with coagulase-negative staphylococci being the most common followed by *Staphylococcus aureus*[4–7]. Depending on the local epidemiology, the percentage of methicillin-/oxacillin-resistant staphylococcal strains vary widely. Other causative agents are anaerobes such as *Peptostreptococcus* spp. and *Cutibacterium* (formerly *Propionibacterium*) spp., gram-negative rods (Enterobacterales, *Pseudomonas aeruginosa*), streptococci and enterococci[8,9]. Fungi and mycobacteria are considered very rare pathogens in infections after ACL-R. Culture negative infections after ACL-R have been described in up to 15-30 % of cases[6,10].

Most common causative pathogens of infections after ACL-R are coagulase-negative staphylococci and *S. aureus*. Therefore, these bacteria should be considered for empiric antibiotic treatment. Other pathogens include anaerobes, gram-negative rods, streptococci and enterococci.

2. What are the routes of infection?

Although evidence of the microorganisms' origin is limited, most of the infections after ACL-R are acute postoperative infections[11]. The route of infection in these cases is perioperative contamination. Several studies have focused on graft colonization during preparation. Harvesting has also given rise to concern about colonization through touching patients' skin or hair follicles[12]. These studies have found similar results with microbial growth in 15-30% of graft cultures[12–14]. Colonization as source of infection is a theory that has not been completely validated. In fact, the rates of colonization are much higher than the rates of infection. However, the "contaminants" described in the aforementioned studies match the most common pathogens after ACL-R, i.e., coagulase-negative staphylococci, *S. aureus* and *Cutibacterium* spp. [13,15]. Moreover, Gavriilidis et al. showed that although none of the 10% of cases with documented colonization developed clinically evident infection during the 24 weeks of follow-up, they had higher inflammation markers than the control group in the postoperative course[16]. The long-term outcome and the potential for the occurrence of delayed low-grade infections is not known for these patients.

Although every joint is at risk of hematogenous seeding during bacteremia- irrespective of previous surgery or present implants- to our knowledge no case of hematogenous infection of joints after ACL-R has been described in the literature and this route of infection appears to be extremely rare.

Recurrence or persistence of infection after ACL-R have been described and can be related to improper debridement, an infected Baker cyst or incorrect surgical treatment in accordance to the staging by Gächter[17]. Those very few case-reports about chronic infections were due to either the same bacteria (mostly coagulase-negative staphylococci)[18] or fastidious and rare microorganisms (mycobacteria, fungi, etc.)[19,20].

Most infections after ACL-R are due to perioperative contamination. Graft harvesting and preparation seem to be a plausible source of contamination.

RISK FACTORS & PREVENTION

3. Which risk factors have been related to infection after ACL-R?

A previous intraarticular corticoid injection has been clearly related to a high risk of infection after ACL-R [21–23]. The odds ratio for infection after ACL-R for those with a history of steroid injection is up to 27 times higher than those without[22]. There are two theories about this risk factor. It is either the immunosuppression produced by the corticosteroid itself or the contamination during puncture (or both combined)[23]. Indeed, prolonged oral steroids or immunosuppression have been associated with higher risk of infection[10]. Additional surgical procedures during the intervention such as meniscal suture, multiligamentous injuries or extraarticular manipulations pose also at greater risk of infection[22,24].

Professional athletes have been seen to have a higher risk of infection after ACL-R according to Sonnery-Cottet[2]. However, there is concern about the possible bias related to athletes as more serious injuries and previous joint injections are often seen in this population. Recently, a prospective cohort study has shown that athletes do have equal risk for infection after ACL-R.[25]

A recent metanalysis of PJI risk after previous corticosteroid injection suggested that there is no longer increased risk of postinterventional infection 6 months (or more) after injection[26]. Hence, the 6 months interval has been recommended in patients scheduled for total knee arthroplasty.

Diabetes, gender and graft type have not been found to be a consistent risk factor for infection after ACL-R[21,27–29].

Confirmed risk factors for infection after ACL-R are previous corticosteroid injection and concomitant surgical procedures. Hence, we recommend to perform all steps under sterile

conditions and with utmost caution to prevent unnoticed contamination. Intraarticular injections up to 6 months prior to ACL-R should be avoided.

4. What is the value of staphylococcal decolonization as a preventive strategy to avoid infection after ACL-R?

Skin and nose decolonization have become popular among orthopedics in recent years[30]. In a recent metanalysis, Weiser et al. stated that it may reduce staphylococcal infections when the carriers are treated before total hip or knee arthroplasty[31]. In addition, economic studies suggest that universal decolonization is cost-effective when compared to screening and treating both permanent and intermittent carriers[32,33]. This is because up to 30% patients are intermittent carriers that are not identified when they are only screened once[33]. All these studies have been performed in the prosthetic field with patients with an average age of around 70 years old. Most of the studies focused on *Staphylococcus aureus* in their evaluation. They did not consider coagulase-negative staphylococci even though this is a frequent pathogen in PJI. When it comes to infections after ACL-R, no study about decolonization has been done. The infection rate after ACL-R is lower than in PJI (even lower if the vancomycin soaking technique of the graft is used)[34]. Therefore, cost-effectiveness could hardly be achieved. However, a 3-day universal decolonization can be considered as a clinical benefit without harm. A reduction in infections in multiligamentous procedures may be expected.

A 3-day skin and nasal universal decolonization prior to ACL-R can be considered in all hospitals in which it can be implemented, taking into account that this recommendation might not be cost-effective.

5. Should intravenous antibiotic prophylaxis be administered before ACL-R?

There is strong evidence in favor of intravenous antibiotic prophylaxis in joint replacement surgery and fracture fixation surgery[35,36]. AlBuhairan et al showed in a pooled analysis of 7 studies with 3,065 total joint arthroplasties, that a single dose of cephalosporin administered between 30 and 60 minutes before incision produces a reduction of the relative risk by 81%[37]. There is conflicting data about prolonged antibiotic prophylaxis after surgery, but it is clear that prolonging it to more than 24 hours increases the side effects (such as microbiota) and can even increase the infection rate[38,39]. There is paucity of studies that have evaluated the effectiveness of intravenous antibiotic prophylaxis in ACL-R. However, Armstrong et al. and Carney et al. have found less infections in the antibiotic prophylaxis group[22,40]. The World Health Organization (WHO) recommends antibiotic prophylaxis when a considerable amount of hardware is to be implanted even though it does not specify if ACL-R belongs to this group[41]. Our recommendation for this matter is to give only one single dose of a

cephalosporin 30 to 60 minutes before incision, i.e., cefazolin 2g (body weight >120kg: 3g) or cefuroxime 1.5g (body weight >120kg: 3g). Although the screws or button can be considered as small implants, the graft is avascular and therefore it behaves like a foreign body. Since most ACL-R are performed on an outpatient basis, only a single dose of antibiotic prophylaxis is the most feasible option. Oral postoperative antibiotics must be avoided because of side effects, low bioavailability and the consequent lack of efficacy[29,39]. In cases of type 1 allergy to penicillins or cephalosporins, prior knee infection, hospitalization or antibiotic therapy, and known MRSA carriers, antibiotic prophylaxis may be switched to one dose of 1g of vancomycin (or 15 mg/kg, max. 2500 mg).

We recommend one single dose of a cephalosporin 30 to 60 minutes before ACL-R or one dose of 1 gram of vancomycin in cases of type 1 allergy, prior knee infection, prior hospitalization or prior antibiotic therapy and known MRSA carriers. Postoperative antibiotic (either intravenous or oral) is not recommended.

DIAGNOSIS

6. What are the clinical signs and symptoms that should raise suspicion of infection after ACL-R?

The signs and symptoms suggestive of infection are often subtle and may be difficult to distinguish from the normal healing process after ACL-R. Increasing or persistent knee pain, tenderness upon slight percussion of the joint, recurrent or persistent knee effusion and systemic symptoms such as fever (> 38.3° C), chills and malaise should call for further investigation[42,43]. However, they are not specific and may also occur in noninfected patients with a large hematoma. Delayed range of motion (ROM) recovery, increased difficulties with physical therapy, increased warmth or swelling, drainage from the incision site/portals (most commonly affected is the tibial tunnel) or any untoward event are suggestive but not specific for infection[5,24,43].

The challenge of late and delayed infection is the indolent presentation of microbial biofilms involving pathogens of low virulence and hence low-grade inflammation[43]. In case of patients presenting with chronic pain after ACL-R, arthrofibrosis is highly suggestive of chronic infection[44].

Purulent secretion, a sinus tract or intraoperative detection of intraarticular pus are confirmative signs of infection[1].

Suggestive signs and symptoms are increased warmth or swelling, wound drainage, arthrofibrosis and delayed ROM recovery, as well as unusual pain and systemic symptoms such as fever and malaise. Confirmative signs are purulent discharge/aspirate, sinus tract communication with the joint and intraoperative intraarticular pus.

7. What is the value of systemic inflammatory markers in the diagnosis of infections after ACL-R?

The specificity of systemic inflammatory markers such as an increased peripheral white blood count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) was found to be limited in the setting of suspected septic arthritis[45]. Furthermore, the sensitivity of systemic inflammatory parameters varies widely between acute and chronic low-grade infections after ACL-R. Only including obvious and florid infections after ACL-R, several studies showed a high sensitivity for CRP[46]. Extrapolated from PJI, infections caused by low-virulent pathogens such as *Cutibacterium* are expected to cause normal or only mildly elevated CRP in the majority of cases[47]. CRP was shown to be more sensitive and specific for the diagnosis of infection than ESR[48], which is not performed anymore in many institutions in the setting of septic arthritis[49]. The CRP course after ACL-R varies widely between individuals and type of surgery performed[50]. Margheritini *et al.* proposed that a CRP value that does not decrease to normal within 2 weeks of intervention or a secondary CRP rise after an initial decrease are suggestive of infection[49]. However, Ruiz-Ibán observed elevated CRPs showing up to a fivefold increase within the first month after ACL-R in uninfected cases. They suggest that a 10-fold increase is very specific for infection (98 % on the 4th postoperative day and 96 % on the 7th postoperative day). One should bear in mind that resorption of hematoma can also cause a high or secondarily increasing CRP.

We recommend performing CRP as a systemic inflammatory parameter. However, it should be interpreted with caution. We expect high sensitivity in acute infection conditions and low sensitivity with chronic infections. A normal CRP does not exclude infection. Neither does an elevated CRP confirm infection. A secondary increase in CRP in the postoperative course is suggestive of infection as is a 10-fold elevation of the normal value in the first postoperative week.

8. What is the value of imaging in the diagnosis of infections after ACL-R?

Infection after ACL-R is primarily a clinical and laboratory diagnosis. Conventional radiography is useful for fast and reproducible evaluation, differential diagnosis and early signs of graft loosening. Magnetic resonance imaging (MRI) is recommended and may help to identify the site of origin of infection either in the joint or at the tibial bone tunnel. It also helps to exclude other complications that may imitate the signs and symptoms of infection such as graft impingement, graft ruptures, focal arthrofibrosis, infected Baker's cysts or cystic degeneration of the graft. In addition, it may help to confirm whether there was an inadequate primary debridement in the case of an improper synovectomy that shows remaining synovitis or an involved Baker's cyst that was left in place[51].

MRI plays an important role in chronic infections in which osteomyelitis is frequently present and removal of sequestrum may be required.

The value of imaging in infections after ACL-R is secondary. It may be used to exclude other causes of an unfavorable postoperative course and complications as well as to detect insufficient debridement in surgically pretreated patients with an unfavorable course. In chronic infections, it is mandatory to assess bone involvement and the tissue debridement called for.

9. Which analyses of synovial fluid should be done in case of suspected infection?

Arthrocentesis is considered the preferred diagnostic test in the preoperative setting[5,24,43]. Every joint presenting abnormal features suggestive for infection after ACL-R, either in the immediate postoperative course or with new-onset symptoms at a later stage after an uneventful course, should be aspirated if there is an effusion. Antibiotic pretreatment may interfere with the microbiological examination and should be withheld until synovial fluid is harvested. The synovial fluid should be sent for microbiology, leukocyte count and differential, and crystal analysis. In acute infections, empiric antibiotic treatment should be initiated immediately after sampling and not be withdrawn until the culture results or leukocyte count are available[42]. In contrast, in suspected chronic infections it is acceptable to start empiric antimicrobial treatment only after intraoperative sampling.

***Leukocyte count*:** The determination of the leukocyte count and percentage of granulocytes in synovial fluid is the cornerstone in the diagnosis of infections after ACL-R (use ethylenediaminetetraacetic acid (EDTA) tubes to prevent coagulation). Although a leukocyte count consistent with infection is considered confirmative criterion by many authors[4,11], there are no uniform cut-offs of leukocyte counts in synovial fluid in joints after ACL-R. Distinguishing infection from aseptic inflammation in native and prosthetic joints thresholds have been debated for decades. Proposed thresholds vary widely and range from 2.000-10.000/µl in prosthetic joints and 17.500-50.000/µl in native joints[45,52,53]. In infections after ACL-R, low grade infections caused by low-virulent pathogens are common. Therefore, it is not advisable to use the same threshold as proposed for native joints. The use of lower cut-offs to avoid underdiagnosing infection is advocated. Consider that lower counts, especially in chronic infections, do occur. This fact contrasts with most previously published recommendations for infections after ACL-R. They did not take in account the existence of low-grade infections with a low level of inflammation. Furthermore, the physiological course of leukocytes in the synovial fluid is unknown in the postoperative course after ACL-R. There is no established and validated cut-off for absolute counts. However, a normal leukocyte count (< 2.000 /µl) rules out infection in most cases. A granulocytes percentage of >90% showed a high likelihood ratio for infection[43].

Microbiology: Traditionally, conventional culturing on agar plates is considered the gold standard for pathogen detection in septic arthritis[45]. Inoculation of synovial fluid into pediatric blood culture bottles showed a higher diagnostic yield in terms of pathogen detection compared to the

conventional agar plate method in septic arthritis[54]. Gram stains show high specificity but low sensitivity (29 to 50 %) and are inferior to culture methods in septic arthritis[45]. Due to the high specificity, it may be used as a rule-in test in the case of a positive result. In patients pretreated with antimicrobials before joint aspiration with negative culture results, bacterial DNA can be identified by polymerase chain reaction (PCR)[55]. However, PCR cannot be done in synovial fluid inoculated in blood culture bottles.

***Biomarkers*:** Several markers such as synovial fluid glucose, protein and lactate dehydrogenase were assessed in the setting of native joints and none of them have shown promising enough results to enter the guidelines[45]. Several reports suggest that D-lactate assessment in synovial fluid could be a specific and sensitive test for the early diagnosis of bacterial infection of native and prosthetic joints[56–58]. To our knowledge, no studies have been performed on joints after ACL-R. Accordingly, calprotectin and alpha-defensin were evaluated in both native and prosthetic joints[59–61]. However, none of the biomarkers has yet been validated in a representative study for infections after ACL-R.

Crystals: The coincidence of crystal arthropathy and infection in joints after ACL-R is probably low with regards to the population undergoing ACL-R. However, particularly in cases with inconclusive diagnostics and negative cultures in presence of a high leukocyte count it represents a differential diagnosis. Polarized light microscopy should be performed to exclude (concomitant) crystal arthropathy if the clinical signs and symptoms occur at a late stage after an uneventful course.

Every painful or otherwise suspicious joint should immediately be aspirated. Antibiotic treatment should be withheld until synovial fluid has been harvested in acute infections. We recommend determining a leukocyte count and differential (percentage of polymorphonuclear cells) as well as microbiological cultures (inoculated in pediatric blood culture bottles and plated on solid media) of synovial fluid. In cases of acute infection at a later stage after ACL-R, crystal arthropathy should be excluded through microscopy. Additional tests such as molecular tests, D-lactate and other biomarkers are not (yet) considered standard, but experimental.

10. What intraoperative diagnostics should be performed?

Histopathology: To our knowledge, there is no data available on specific histopathological changes in infections after ACL-R. Nevertheless, microscopic tissue changes of the affected joint should be assessed by an experienced histopathologist. In native joints, a synovialitis score was elaborated in order to facilitate the discrimination of rheumatoid, septic and non-septic arthritis[62,63]. Consistent morphology may corroborate the clinical diagnosis of infection in cases of culture-negative infections. In addition, rare differential diagnoses such as crystal arthropathy and mycobacterial septic arthritis

may be excluded. Normal histopathological findings do not exclude (low grade) infection. Additionally, sampling errors might mitigate the real entity.

Microbiology: To collect different types of specimens, we recommend harvesting another intraoperative sample of synovial fluid for culture. In addition, multiple samples of macroscopically affected tissue (synovial lining, graft, femoral and tibial tunnel) should be taken[43]. As extrapolated from PJI, (3 to) 5 tissue samples increase the diagnostic yield and facilitate the interpretation of the results if low-virulent skin commensals are isolated[64].

In cases of removal or exchange of the graft and/or the fixation devices, the graft should be sent for microbiological culture and foreign material (fixation devices) to sonication, if available. Sonication has been shown to be an efficient diagnostic method by dislodging the biofilm from the surface in PJI and implant-associated infections[65,66].

It is important to notify the microbiology laboratory that there is non-vascularized and foreign material involved in the process so that prolonged incubation (for 10 to 14 days) can be carried out and a more extensive interpretation of the results can be elaborated, especially in presence of a typical skin commensal[42]. As used for PJI, isolation of the identic pathogen in at least 2 different samples in cases of low-virulent pathogens (e.g., *Cutibacterium* spp., coagulase-negative staphylococci, *Corynebacterium* spp.) and in one sample in case of high-virulent pathogen is considered significant and confirms infection after ACL-R. In cases of non-significant pathogen detection of low-virulent pathogens (e.g., coagulase-negative staphylococcus in one specimen), the result should be interpreted in the context of non-microbiological criteria.

We recommend collecting and analyzing:

- **Synovial fluid for microbiological analysis (blood cultures bottles and native vials)**
- **3 to 5 intraoperative tissue samples from representative and macroscopically infected tissue**
- **at least one sample for histopathological examination**
- **in case of graft removal/exchange, sending the fixation devices (foreign material) to sonication (if available) and the graft for conventional culture**

The laboratory should be notified about the type of infection and that a foreign body is involved in the infection to ensure prolonged incubation of the samples.

Confirmative criteria for infection after ACL-R are intraarticular purulence, purulent secretion or sinus tract communication with the joint, positive cultures of tissue, synovial fluid or sonication and/or histopathology consistent with acute infection.

11. Should blood cultures be collected in any case of infection after ACL-R?

In general, infections after ACL-R are of perioperative pathogenesis and blood cultures are not needed. However, every joint is at risk of hematogenous seeding in case of (prolonged and high-load) bacteremia irrespective of a previous history of ACL-R. Accordingly, secondary infection can occur at any stage after ACL-R (even years or decades after surgery). It results in an acute infection after ACL-R that occurs after an uneventful course, usually concomitantly with systemic signs and symptoms of bloodstream infection like fever, chills, malaise etc. If hematogenous infection is diagnosed, investigation of cause (i.e., echocardiography, orthopantomogram, urinalysis, conventional lung X-ray etc), depending on the pathogen, is indicated.

In the case of an acute onset of local and systemic signs and symptoms of knee infection at any time after an uneventful period after ACL-R, blood cultures should be collected to exclude hematogenous infection.

CLASSIFICATION

12. What classification of infection after ACL-R should be used in clinical and scientific practice?

Since its first publication 1997, the classification of infection after ACL-R by Williams et al. has been repeatedly proposed for use in clinical and scientific practice. It differentiates between acute (< 2 weeks), subacute (2 weeks up to 2 months) and late (> 2 months) infection after ACL-R[67]. The basis for these intervals is unclear and there is no clinical impact deduced from the different classifications. In addition, acuity and time of occurrence after surgery are mixed in the previously used classification. We propose differentiating between acute and chronic infection as well as taking into account the pathogenesis along with the time of symptom onset. Acute infections arise in the early postoperative period. Hematogenous infections may occur at any time even though they are less frequent in ACL-R than joint replacements and are mostly caused by high-virulent pathogens such as *S. aureus*, streptococci and gram-negative rods. Chronic or low-grade infections occur at a later stage and are primarily caused by low-virulent pathogens like coagulase-negative staphylococci, *Corynebacterium* spp. and *Cutibacterium* spp. While chronic septic arthritis is a rarity in native joints, chronic infections are more common in joints after ACL-R that contain non-vascularized tissue and metal work. In the presence of a foreign material in the joint, the infection is categorized according to the "biofilm age"[52]. Accordingly, periprosthetic joint infections (PJI) with a biofilm less than 3 to 4 weeks of age are considered acute, whereas implant-associated infections exceeding this time interval are categorized as chronic[53,68]. Given the presence of native cartilage, chronic changes may appear earlier than in prosthetic joints and therefore, infections manifesting within 2 weeks after ACL-R are considered to be early/acute. The clinical relevance of this classification is the possible

anticipation of the pathogen and respective choice of empiric antibiotic treatment and type of surgical treatment.

We suggest classifying into acute and chronic infections after ACL-R. In the case of a diagnosis within 2 weeks after ACL-R or the new-onset of symptoms of less than 2-weeks duration, the infection is considered acute. On the other hand, chronic infections manifest at more than 2 weeks after ACL-R or with a symptom duration of more than 2 weeks at any time.

SYSTEMIC ANTIMICROBIAL TREATMENT

Treatment of infections after ACL-R consists of a combination of surgical and antimicrobial therapy. Arthroscopic debridement should be performed as soon as clinical suspicion is established (even if microbiological results are still pending) and is the surgical treatment of choice for the majority of cases. Gächter classification along with graft condition serve as decision aid for selection of the optimal surgical treatment. Graft and hardware must be removed in case of multiple debridement procedure failures and/or hardware loosening/graft insufficiency. We recommend that graft reimplantation be performed after 6 weeks in selected cases in cases of graft and hardware removal.

13. Which antimicrobial agents are recommended for empirical treatment until culture results are available?

To cover the most common pathogens that cause infections after ACL-R, we recommend starting an intravenous (i.v.) antimicrobial treatment with a beta lactam/beta lactam inhibitor combination [e.g., ampicillin/sulbactam 3x3g i.v. or amoxicillin/clavulanic acid 4x2.2g i.v. (or 4x1.2g, depending on availability)] (Table 1). As coagulase-negative staphylococci are oxacillin/methicillin-resistant in the majority of cases (variable epidemiology), the addition of vancomycin (according to through level, target 15 to 20mg/l) or daptomycin 1x8-10mg/kg i.v. is suggested until culture results are available. In case of allergy to penicillin (non-type 1), we suggest replacing the beta lactam antibiotic by a 1st or 2nd generation cephalosporin (e.g., cefazoline 3x2g i.v. or cefuroxime 3x1.5g i.v.). In case of a type 1 allergy (anaphylaxis, Quincke's edema), we suggest using daptomycin 1x8-10mg/kg as a monotherapy. It is preferred over vancomycin due to its bactericidal activity, lack of toxicity and its immediate attainment of therapeutic levels. Regarding the substances used in previous studies, we recommend against the use of (flu-)cloxacillin, 1st or 3rd generation cephalosporins[4,21] due to their narrow spectrum or gentamicin[43] due to its toxicity as an empirical treatment. Indeed, the antimicrobial treatment should be targeted to the pathogen as soon as the causative agent and its susceptibility are known.

We advise against administering rifampin as an empirical treatment as resistance may occur when used improperly.

Table 1. Empiric antimicrobial treatment

1. choice	Non-type 1 penicillin allergy	Type 1 penicillin allergy
Ampicillin/sulbactam 3 x 3 g or Amoxicillin/clavulanic acid 4 x 1.2 - 2.2g PLUS Vancomycin 2 x 15 mg / kg or Daptomycin[a] 1 x 8 mg / kg	Cefazoline 3 x 2g i.v. or Cefuroxime 3 x 1.5 g PLUS Vancomycin 2 x 15 mg / kg or Daptomycin[a] 1 x 8 mg / kg	Daptomycin[a] 1 x 8 mg / kg

[a] Use one of the following doses close to 8 mg/kg: 350 mg, 500 mg, 700 mg, 850 mg, 1000 mg (ampoules contain 350mg or 500mg of daptomycin)

14. When should antimicrobial treatment be started?

As soon as joint fluid has been obtained, prompt intravenous antibiotic therapy should be given in cases with strong clinical evidence of acute infection[5,21,43]. In this situation, microbiology and leukocyte count results should not be awaited. In cases of chronic infection, the decision whether to start antimicrobials before revision surgery or after harvesting samples intraoperatively may be based on leukocyte count. However, there is no validated cut-off to confirm infection to date (see also section “Diagnosis”, Leukocyte count). In the case of a normal leukocyte count, infection is unlikely, and antibiotics should be withheld until intraoperative samples are harvested.

Empirical antibiotic treatment should be initiated immediately after joint aspiration if acute infection is suspected.

15. Is the use of biofilm-active agents indicated in infections after ACL-R?

While no biofilm-active treatment is needed in septic arthritis of the native joint, the use of biofilm-active antibiotics in implant-associated joint infections has been shown to be superior[69]. In infections after ACL-R, a native joint with non-vascularized (graft) and foreign (fixation device) material is involved in infection. Guidelines based on either clinical trials or animal model studies recommend the use of rifampin in combination with another antibiotic for the treatment of staphylococcal infections[70–73] and ciprofloxacin for gram-negative rods[72]. In this context, we recommend using biofilm-active treatment -if available- in the case of treatment scenarios in which the graft is exchanged or retained. Pérez-Prieto et al. showed a high rate of treatment success using a rifampin-fluoroquinolone combination in staphylococcal infections after ACL-R[7]. Based on theoretical considerations and in vitro studies, the same applies to infections caused by cutibacteria[74]. The

optimal time-point for starting rifampin therapy is still debated. We advocate starting rifampin after all drains have been removed and the wound is dry, as recommended for periprosthetic joint infections.

Although clinical evidence is weak, based on theoretical considerations and extrapolation from other implant-associated infections, the use of biofilm-active antibiotics in infections with any grafts and fixation devices in place is advisable.

16. What is the optimal treatment duration for ACL-R-infections?

There is a controversy regarding the duration of antibiotic treatment and when to switch from intravenous to oral therapy. There are no randomized controlled studies addressing this issue. In native septic arthritis, the duration of antimicrobial treatment depends on the organism isolated and the clinical response to the chosen antibiotic. The duration of treatment is generally 2 to 6 weeks[75]. In infections after ACL-R, it was 2 to 12 weeks in previously published case series[6,11]. Intravenous treatment was given for 5 days to 6 weeks[7,11,76]. In most reports, an adequate clinical response and a decrease in C-reactive protein (CRP) are prerequisite for a switch to oral treatment or discontinuation of antibiotics[6,43,76,77]. Overall, antibiotic treatment is maintained for a minimum of 4 to 6 weeks[5,11,42,43,67]. In a recent study, a good clinical outcome was seen with oral treatment started at a mean of 5 days (range, 4–7) after surgery and a total antibiotic treatment lasting an average of six weeks[7]. Recent landmark studies corroborated the trend towards shorter i.v. treatment durations in severe infections such as bone and joint infections and infective endocarditis[78,79].

A 1-week (up to 2 weeks) i.v. treatment regimen is suggested. It should be followed by oral treatment for another 4 to 5 weeks. It would be preferable to do it with bactericidal agents with good bioavailability and bone penetration as well as biofilm-activity if avascular tissue and fixation devices are in situ. The conditions for switching to an oral treatment are a good clinical response with a decrease in local inflammatory signs and CRP trending towards normal values.

We suggest a 1 week (up to 2 weeks) of intravenous treatment followed by oral treatment for another 4-5 weeks, preferably with bactericidal agents with good bioavailability and bone penetration as well as biofilm-activity if avascular tissue and fixation devices are in situ. The conditions for switching to oral treatment are a good clinical response with nearly normal CRP values.

17. What is the recommended targeted antimicrobial regimen for the most common pathogens?

The recommended pathogen-specific treatment extrapolated from the treatment of septic arthritis and periprosthetic joint infections are shown in Table 2[53,75,80]. In culture negative cases, we advise giving broad spectrum (i.e., empiric) intravenous antibiotics followed by a biofilm-active combination covering the most common pathogens, i.e., rifampin and fluoroquinolones (see below).

Table 2. Targeted antimicrobial treatment.

Microorganism	**Antibiotic** (check pathogen susceptibility before)	**Dose** (*renal adjustment needed)	**Route**
***Staphylococcus* spp.**			
- Oxacillin-/methicillin-susceptible	Flucloxacillin[a]	4 x 2g*	i.v.
	or		
	Cefazoline	3 x 2g*	i.v.
	+/- Fosfomycin[c]	3 x 5g*	i.v.
	for 1-2 weeks*, followed by (according to susceptibility)		
	Cotrimoxazole	3 x 960mg*	p.o.
	or		
	Rifampin[d] +	2 x 450mg	p.o.
	Levofloxacin or	2 x 500mg*	p.o.
	- Cotrimoxazole or	3 x 960mg*	p.o.
	- Doxycycline or	2 x 100mg	p.o.
	- Fusidic acid	3 x 500mg	p.o.
- Oxacillin-/methicillin-resistant	Daptomycin[e] or	1 x 8mg/kg*	i.v.
	Vancomycin[b]	2 x 15mg/kg*	i.v.
	+/- Fosfomycin[c]	3 x 5g*	i.v.
	for 1-2 weeks*, followed by an oral therapy as above		
***Streptococcus* spp.**	Penicillin G[a] or	4 x 5 million U*	i.v.
	Ceftriaxone	1 x 2g	i.v.
	for 1-2 weeks*, followed by:		
	Amoxicillin or	3 x 1000mg*	p.o.
	Doxycyclin	2 x 100mg	p.o.
***Enterococcus* spp.**			
- Penicillin-susceptible	Ampicillin or Amoxicillin	4 x 2g*	i.v.
	+ Gentamicin[f] or	1 x 3mg/kg*	i.v.
	+ Ceftriaxone[g]	2 x 2g	i.v.
	+/- Fosfomycin[c]	3 x 5g*	i.v.
	for 1-2 weeks*, followed by:		
	Amoxicillin	3 x 1000mg*	p.o.
- Penicillin-resistant or allergy to penicillin	Vancomycin[b] or	2 x 15mg/kg*	i.v.
	Daptomycin[e]	1 x 10mg/kg*	i.v.
	+ Gentamicin[f]	1 x 3mg/kg*	i.v.
	+/- Fosfomycin[c]	3 x 5g*	i.v.
	for 1-2 weeks, followed by:	2 x 600 mg	p.o.
	Linezolid		
Gram-negative rods			

- Enterobacterales (*E. coli, Klebsiella* spp., *Proteus* spp. etc.)	Ceftriaxone or Piperacillin/tazobactam or Meropenem for 1-2 weeks followed by: Ciprofloxacin	1 x 2g 3 x 4.5g* 3 x 1g* 2 x 750mg*	i.v. i.v. i.v. p.o.
- Nonfermenters (*Pseudomonas aeruginosa, Acinetobacter* spp.) or *Enterobacter* spp.	Piperacillin/tazobactam or Meropenem or Ceftazidime or Cefepime + Tobramycin[h] (or Gentamicin) for 2 weeks, followed by: Ciprofloxacin p.o.	4 x 4.5g* 3 x 2g* 3 x 2g* 1 x 3-5mg/kg* (1 x 3mg/kg)* 2 x 750mg*	i.v. i.v. i.v. i.v. i.v.
Anaerobes - Gram-positive (*Cutibacterium, Peptostreptococcus, Finegoldia* spp.)	Penicillin G[a] or Ceftriaxone for 1-2 weeks, followed by: Rifampin[d] + Levofloxacin or Amoxicillin	4 x 5 million U* 1 x 2g 2 x 450mg 2 x 500mg* 3 x 1000mg*	i.v. i.v. p.o. p.o. p.o.
Candida spp. - Fluconazole-susceptible	Caspofungin[i] Anidulafungin for 1-2 weeks, followed by: Fluconazole	1 x 70mg 1 x 100mg (1. day 200 mg) 1 x 400mg*	i.v. i.v. p.o.
- Fluconazole-resistant	Individual (e.g. voriconazole[j] 2 x 4mg/kg p.o.)		
Culture-negative	Ampicillin/sulbactam[a] for 2 weeks, followed by: Rifampin[d] + Levofloxacin	3 x 3g* 2 x 450mg 2 x 500mg*	i.v. p.o. p.o.

[a] Non-type 1 **penicillin allergy** (e.g. skin rash): cefazolin (3x2g i.v.). In the case of anaphylaxis (type 1 allergy such as Quincke´s edema, bronchospasm, anaphylactic shock) or cephalosporin allergy: vancomycin (2x15mg/kg i.v.) or daptomycin (1x8mg/kg i.v.); Ampicillin/sulbactam is equivalent to amoxicillin/clavulanic acid (4x2.2g i.v.)

[b] Check **vancomycin** through concentration (take blood before next dose) at least 1x/week; First concentration before 4th dose; therapeutic range: 15-20µg/ml

[c] Fosfomycin can be given 3x5g or 2x8g. Fosfomycin is not available in all countries and not in the same dosage. Monitor regularly serum electrolytes

[d] Add it already to intravenous treatment as soon as wounds are dry and drains removed and the graft is retained or exchanged; in patients aged >75 years, rifampin is reduced to 2x300mg p.o.

[e] Use one of the following doses close to 8 or 10mg/kg (depending on pathogen): 350 mg, 500 mg, 700 mg, 850 mg, 1000 mg (ampoules contain 350mg or 500mg of daptomycin)

[f] Give only, if enterococcus is tested **gentamicin high-level (HL)** susceptible (consult microbiology laboratory). In gentamicin HL-resistant *E. faecalis*: gentamicin is exchanged with ceftriaxone (2x2g i.v.)

[g] Only for *Enterococcus faecalis*

[h] Combination treatment only indicated in multi-resistant gram-negative bacteria

[i] After a loading dose of 70mg on day 1, **reduce to 50mg** in patients weighing <80kg from day 2

[j] Loading dose 2x6mg/kg, then 2x4mg/kg, measure through level (1-5µg/ml)

SUMMARY OF RECOMMENDATIONS

Microbiology, pathogenesis and prevention

- Most common causative pathogens of infections after ACL-R are coagulase-negative staphylococci and *S. aureus*. Therefore, these bacteria should be considered for empiric antibiotic treatment. Other pathogens include anaerobes, gram-negative rods, streptococci and enterococci.
- Most infections after ACL-R are due to perioperative contamination. Graft harvesting and preparation seem to be a plausible source of contamination, hence we recommend to perform all steps under sterile conditions and with utmost caution to prevent unnoticed contamination.
- Confirmed risk factors for infection after ACL-R are previous injections and concomitant surgical procedures. Hence, we recommend to perform all steps under sterile conditions and with utmost caution to prevent unnoticed contamination. Corticosteroid injection should be avoided for at least 6 months before ACL-R.
- A 3-day skin and nasal universal decolonization prior to ACL-R may be considered in all hospitals in which it can be implemented, taking into account that this recommendation might not be cost-effective.
- We recommend one single dose of a cephalosporin 30-60 minutes before ACL-R or one dose of 1 gram of vancomycin in cases of type 1 allergy, prior knee infection, prior hospitalization or prior antibiotic therapy. Postoperative antibiotic (either intravenous or oral) prophylaxis is not recommended.

Diagnosis

- Suggestive signs and symptoms are delayed ROM recovery, increased warmth or swelling, wound drainage and arthrofibrosis as well as unusual pain and systemic symptoms such as fever and malaise. Confirmative signs are purulent discharge/aspirate, sinus tract communication with the joint and intraoperative intraarticular pus.
- We recommend performing CRP as a systemic inflammatory parameter. However, it should be interpreted with caution. We expect high sensitivity in acute infection conditions and low sensitivity with chronic infections. A normal CRP does not exclude infection. Neither does an elevated CRP confirm infection. A secondary increase in CRP in the postoperative course is suggestive of infection as is a 10-fold elevation of the normal value in the first postoperative week.

- The value of imaging in infections after ACL-R is secondary. It may be used to exclude other causes of an unfavorable postoperative course and complications as well as to detect insufficient debridement in surgically pretreated patients with an unfavorable course. In chronic infections, it is mandatory to assess bone involvement and the tissue debridement called for.
- Every painful or otherwise suspicious joint should immediately be aspirated. Antibiotic treatment should be withheld until synovial fluid has been harvested. We recommend doing a leukocyte count and differential (percentage of polymorphonuclear cells) as well as microbiological cultures (inoculated in pediatric blood culture bottles and plated on solid media). In cases of acute infection at a later stage after ACL-R, crystal arthropathy should be excluded through microscopy. Additional tests such as molecular tests, D-lactate and other biomarkers are not (yet) considered standard, but experimental.
- We recommend collecting and analyzing:
    - Synovial fluid for microbiological analysis (blood cultures bottles and native vials)
    - 3 to 5 tissue samples from representative and macroscopically infected tissue
    - at least one sample for histopathological examination
    - in case of graft removal/exchange, sending the fixation devices (foreign material) to sonication (if available) and the graft for conventional culture

  The laboratory should be notified about the type of infection and that a foreign body is involved in the infection to ensure prolonged incubation of the samples.
- Confirmative criteria for infection after ACL-R are intraarticular purulence, purulent secretion or sinus tract communication with the joint, positive cultures of tissue, synovial fluid or sonication and/or histopathology consistent with acute infection.
- In the case of an acute onset of local and systemic signs and symptoms of knee infection at any time after an uneventful period after ACL-R, blood cultures should be collected to exclude hematogenous infection.

Classification

- We suggest classifying into acute and chronic infections after ACL-R. In the case of a diagnosis within 2 weeks after ACL-R or the new-onset of symptoms of less than 2-weeks duration, the infection is considered acute. On the other hand, chronic infections manifest at more than 2 weeks after ACL-R or with a symptom duration of more than 2 weeks at any time.

Systemic antimicrobial treatment

- We recommend performing arthroscopic debridement in combination with antibiotic therapy as the primary therapeutic option in every patient.
- Empirical antibiotic treatment should be initiated immediately after joint aspiration if acute infection is suspected.
- Although clinical evidence is weak, based on theoretical considerations and extrapolation from other implant-associated infections, the use of biofilm-active antibiotics in infections with any grafts and fixation devices in place is advisable.
- We suggest a 1 week (up to 2 weeks) of intravenous treatment followed by oral treatment for another 4-5 weeks, preferably with bactericidal agents with good bioavailability and bone penetration as well as biofilm-activity if avascular tissue and fixation devices are in situ. The conditions for switching to oral treatment are a good clinical response with nearly normal CRP values.

ACKNOWLEDGEMENTS

All authors declare that they have no conflict of interest related to this study. There are no funding sources to report.

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HIGHLIGHTS

- Every painful joint after ACL-R should be aspirated
- Most common pathogens of infections after ACL-R are staphylococci
- Arthroscopic debridement and antibiotics are treatment of choice for infections after ACL-R
- The use of biofilm-active antibiotics is advisable if grafts and fixation devices are in place