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Periprosthetic Knee Infection: From Diagnosis to Surgery

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Abstract: Periprosthetic joint infection (PJI) is one of the major complications resulting from the implantation of a joint prosthesis. Staphylococci are responsible for more than 50% of prosthetic infections, about 20% can be polymicrobial, 15% are gram-negative and about 10% of cultures are negative. The complete eradication of the infection is extremely difficult. For a correct treatment is first of all useful to perform a clinical staging based on the anatomical location of the infection and on the immune characteristics of the host. However, regardless the area of infection, the role of the surgeon is crucial, firstly in terms of timing and secondly in assessing the degree of invasiveness of the infected and necrotic tissues required. The goal of the treatment must be to eradicate the infection ensuring the maximum functional result.

Keywords: TKA; Infection; PJI

1. Introduction

Periprosthetic joint infection (PJI) is one of the major complications resulting from the implantation of a joint prosthesis. The incidence of a first implant prosthetic infection is 1-2%, which reaches 4% in revisions [1–3].

There is no universally accepted definition of a prosthetic joint infection. Clinically, it manifests itself in various forms and the classic signs of an infection such as fever, leukocytosis or local signs, may be absent, making diagnosis difficult. However, failing to identify the pathogen does not rule out the diagnosis.

Staphylococci are responsible for more than 50% of prosthetic infections, about 20% can be polymicrobial, 15% are gram-negative and about 10% of cultures are negative [4,5].

It has been seen that the pathogens are different depending on the time of onset of the infection compared to surgery [6,7].

In particular, it has been seen that infections that develop within the first 4 weeks after surgery (Early infection) are caused by highly virulent microorganisms (e.g., Staphylococcus aureus), while those that develop after 3 months are caused by low virulence organisms such as coagulase-negative Staphylococcus, Propionibacterium acnes and Enterococci.

Infection rates are higher in the first 2 years after surgery due to the greater vascularization of the peri-implant tissues which favors the hematogenous spread of the infection [8].

The complete eradication of the infection is extremely difficult especially for the biofilm, a complex environment formed by bacteria within their extracellular matrix, capable of evading the body's immune defenses, thus creating a resistance to antibiotics that is 1000 times higher than normal [9].The most relevant points on prosthetic infections were discussed during the International Consensus held Philadelphia, in 2018, in order to give indications in relation to the latest publications.

For a correct treatment is first of all useful to perform a clinical staging based on the anatomical location of the infection and on the immune characteristics of the host.

However, regardless the area of infection the role of the surgeon is crucial, firstly in terms of timing and secondly in assessing the degree of invasiveness of the infected and necrotic

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tissuesrequired. In fact, not only the probabilities of recurrence, for example due to infectious foci left in place and post-operative complications, depend on the appropriateness and correctness of the surgical act, which must in any case be timely, but also the healing itself represented by bone's stabilization and the restoration of joint and muscle function.

Few articles have been published on the management of exposed prostheses, but it seems that in most cases, adequate and early soft tissue coverage allows the prosthesis to be saved [10].

Skin complications are common following knee replacement surgery, although they do not always lead to exposure of the implant. In case of exposure, the simple suture is ineffective and only a vascularized graft makes it possible to heal the wound and save the prosthesis.

The gastrocnemius muscle flap is the technique of choice for its simplicity and safety, associated with local and systemic antibiotic therapy, allowing good quality coverage. It can be performed in a single step and low morbidity and no residual scarring are reasons for doing it early [11–13].

Other advantages of this method are early mobilization and quick hospital stays [11]. It also reduces the rate of arthrodesis with better functional results.

2. Diagnosis

To date, the diagnosis of PJI represents a challenge, although over the years new criteria and scores have been developed that make diagnosis much easier than in the past.

Proper PJI diagnosis remains critical for success and choosing the optimal treatment option [14].

In 2011, the Musculoskeletal Infection Society (MSIS) proposed criteria to standardize the diagnosis of PJI [15], which were then revisited in 2013 during the International Consensus Meeting (ICM) [16].

Recently, national and international workgroups have convened to establish standardized diagnostic protocols for suspected PJI. Most recently, a new 2018 evidence-based PJI definition has been published, which demonstrates improved performance for diagnosing hip and knee PJI on formal external validation [17]. The latest definition of PJI with a practical guide for clinicians, based on a three-level approach was released by the European Joint Infection Society (EBJIS) by the end of 2020 [18].

First of all, in the presence of a communicating fistula as well as in case of frank exposure, the TKA is definitely considered infected.

In occult cases, local signs of infection or fever can lead to suspicion of prosthesis infection, but pain is the most relevant symptom, present in over 90% of cases.

As first level tests we use the **X-rays** in two projections, blood tests and arthrocentesis.

To date, there is no clinical sign that, alone, is able to make a 100% diagnosis.

X-rays may show signs of prosthesis loosening and femoral or tibial osteolysis (radiolucent lines).

In the **blood**, on the other hand, the levels of C-reactive protein **(CRP)** and / or **D-dimers**, and the erythrocyte sedimentation rate **(ESR)** are measured.

However, recent studies on the sensitivity of CRP and ESR have calculated around 20% of false negatives [19].

In case of **fever (>38 °C)**, before any antibiotic treatment, it is recommended taking **blood cultures** in order to diagnose early stage bacteremia and avoid worse complications such as septic shock, SIRS or MOF.

Another important diagnostic step is the knee **arthrocentesis** with suspected infection to be performed in a sterile environment.

If possible, any antibiotic therapy should be suspended for at least 14 days to increase the sensitivity of the test [20].

It would be recommended to take at least 2 mL of liquid in order to perform the various tests (Alpha-defensin test and dosage of WBC, LE (leukocytes), CRP and PMN (%) in the synovial fluid.

Alpha-defensin is an antimicrobial peptide produced by neutrophils and together with CRP represents one of the new markers included in the diagnostic criteria. This could be a very accurate

 doi:10.20944/preprints202408.1663.v2

test but has limitations, such as high costs, it is not indicated in the immediate postoperative period and could give false positives for metallosis.

Stone et al. [21] proposed an algorithm that combines the alpha defensin test with the CRP assay to reduce false positives and false negatives.

Some tests can be done directly at the patient's bedside at the collection site. The cheapest and fastest is the leukocyte esterase dip stick test (LET), which is strongly positive (+ +) in the case of a deep purple color. In case of positivity, a differential diagnosis should be made with other inflammatory arthropathies (e.g., gout, rheumatological diseases, etc.) In a meta-analysis of 1,011 patients, a sensitivity of approximately 90% and a specificity of approximately 97% was shown [22].

However, tests performed on synovial fluid samples sent to the laboratory, centrifuged to remove blood traces, are more reliable. In a recent study the cutoffs considered for the diagnosis of PJI are 1630 leukocytes / microL (SE 83.6%, SP 82.2%) and PMN (%) of 60.5% (SE 80.3%, SP 77.1%) [23]. However, there are still no universally recognized values. It is now recognized that swab culture tests provide a high percentage of false positives. The **gold standard** for diagnosing PJI is **bacterial cultures**, which should be grown in a microbiology laboratory for at least 14 days. At least 2 positive cultures for the same microorganism are indicative of infection. Based on these tools, a scoring system for the diagnosis of PJI was created at an international meeting held in Philadelphia in 2018. This new score system facilitated the preoperative diagnosis and, compared to the MSIS criteria, demonstrated an improvement in results with a sensitivity of 97.7% and a specificity of 99.5%.

In complex diagnostic situations, periprosthetic tissue biopsy can provide crucial information. This procedure, usually performed under CT or Ultrasound guidance, allows the collection of tissue samples for histopathological analysis and culture. The presence of inflammatory cell infiltrates and positive culture are indicative of infection.

The last frontier for the diagnosis of PJI is represented by **next-generation sequency**, a new application of genetic sequencing with lower costs and faster times than the classical technique [24]. This technique has proved to be extremely sensitive, so much so as to detect bacterial DNA even in the original joints [25]. However, the study on the application of this technique is still in its infancy.

Table 1.

Major criteria (at least one of the following)	Decision
2 positive cultures of the same organism	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

Table 2. New scoring system definition for PJI (Philadelphia ICM 2018). Caution is required in several conditions, like adverse local tissue reaction, crystal deposition disease, slow growing organisms, etc. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LE, leukocyte esterase; PMN, polymorphonuclear; WBC, white blood cell.

		Minor criteria	Score	Decision
Preoperative Diagnosis	Serum	Elevated CRP or D-Dimer	2	≥6 Infected
		Elevated ESR	1	
		Elevated synovial WBC count or LE	3	**2-5 Possibly Infected**[a]
	Synov	Positive alpha-defensin	3	
		Elevated synovial PMN (%)	2	0-1 Not Infected
		Elevated synovial CRP	1	

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	Inconclusive pre-op score or dry tap	Score	Decision
Intraoperative Diagnosis	Preoperative score	-	≥6 Infected
	Positive histology	3	
	Positive purulence	3	**4-5 Inconclusive[b]**
	Single positive culture	2	≤3 Not Infected

3. Treatment

The treatment of knee prosthesis infections must take into account various aspects, such as: the timing of onset (early/ delayed/ late infection), the condition of the soft tissues and the clinical objectivity of the infectious picture (the functionality of the extensor apparatus [26,27]), the patient`s comorbidities, laboratory (inflammation indices) and microbiological aspects (the agent/ etiological and relative antibiotic sensitivity), the stability of the prosthetic implant (condition of the implant) , the patients expectations and the functional needs.

The goal of the treatment must be to eradicate the infection ensuring the maximum functional result. It includes antibiotic therapy, as the only treatment or in combination to surgical therapy.

3.1. The Antibiotic Therapy

The antibiotic therapy is one of the two fundamental pillars in the treatment of prosthetic infections. In case of infection of the surgical wound only, it may represent the treatment of choice in the absence of surgical treatment. In the case of infection, not limited to the surgical wound alone , the efficiency of eradicating the infection with antibiotic therapy alone is limited mainly due to the presence of the bacterial biofilm on the prosthetic implant, therefore its use should be limited to specific circumstances, such as high operative risk, in the medically stable patient (absence of an ongoing septic picture), the presence of low virulence microorganisms sensitive to antibiotics oral, mechanically stable prosthesis [28].

Based on the organism grown on culture the specific antibiotic should be given as such. Broad-spectrum antibiotics should be prescribed and used in case of an acutely knee infection of a patient showing signs of sepsis [29].

Monitoring the patient during treatment and deciding the type and course of the antibiotic should be determined by a medical microbiologist and virologist specialist. Post surgery, a protocol should be put in place in order to follow the duration and route of administering the prescribed antibiotic.

3.2. Surgical Treatment

In our clinical case, the treatment had also to consider the problem of exposure of the prosthetic implant, in addition to the infectious problem. In association with the antibiotic treatment, the surgical treatment can make use of several options with different clinical outcome: from rescue procedures (arthrodesis, amputation) to procedures with preservation of joint function (one/two stage revision), DAIR (debridement antibiotic treatment and implant retention).

3.2.1. DAIR and DAPRI

In early infection, the debridement and irrigation with antiseptic solutions, without implant removal, are usually the choices for surgical treatment, in the absence of signs X-rays of mobilization of the prosthetic implant (to be confirmed intraoperatively) or of heterotrophic bone formation (radiographic signs of chronicity of the infection) [28]. The tissue removed during the debridement

 doi:10.20944/preprints202408.1663.v2

phase is sent for cultures. The application of a drain can facilitate the expulsion of any postoperative intra-articular blood serum collections and finally the local application of antibiotics in beads, in association with the systemic one can ensure a better postoperative antibiotic coverage.

In the presence of moving parts, the treatment should include the replacement of each modular component of the system) [30]. The DAIR can represent a valid surgical option even in the presence of mega-prostheses and sufficient covering tissue to endure adequate post-operative closure. The DAIR should be performed within 4 weeks surgery, before the biofilm is formed in the prosthetic implant. Contraindications are represented by: the chronic infections with signs of implant loosening, covering defects, patients not eligible for reoperation.

Advantages of DAIR:

- Less invasive than complete removal and replacement of the prosthesis.
- Lower risk of surgical complications.
- Reduction of costs associated with the surgery.

Limitations of DAIR:

- Risk of persistence or recurrence of the infection.
- Possible failure if the infection is chronic or the implant is unstable.

DAPRI is an evolution of DAIR, with a crucial addition: partial implant replacement. This approach includes:Debridement As in DAIR, careful removal of infected tissue is essential; Antibiotic management follows the same principles as DAIR, with the need for prolonged and targeted therapy; Prosthesis Retention: Unlike DAIR, DAPRI involves the replacement of some components of the implant, typically the modular components (such as the polyethylene liner), keeping the fixed parts intact if they are not compromised; Partial Implant Replacement: This step allows the removal of the prosthetic components most exposed to infection, reducing the risk of recurrence and improving infection control.

Advantages of DAPRI:

- Greater control of infection compared to DAIR.
- Conservation of the prosthesis, reducing invasiveness compared to total revision.
- Reduced risk of post-operative prosthetic instability.

Limitations of DAPRI:

- More complex and technically demanding procedure compared to DAIR.
- Need for an accurate assessment of the stability of the remaining implant.

3.2.2. Two-Stage Revision

The prosthetic implant and any other foreign material are removed in the first stage. An aggressive debridement of all necrotic tissues is performed and an antibiotic spacer is implanted to allow the healing of the injured tissues and the total or partial preservation of joint motility.

The second stage involves the removal of the antibiotic spacer and implantation of a new prosthesis, after the eradication of the infection [30].

The two-stage review is indicated in the case of chronic infections with mobilization of the implant and for infections caused particularly by virulent organisms such as MRSA [28].

3.2.3. Single Stage Revision

The use of a single stage revision is recommended in patients with a known aetiologic organism and sensitive to an antibiotic when no infectious collections are present and when the patient is not immunocompromised, an there is no radiological evidence of prosthetic implant loosening or ongoing osteitis [28]. This type of revision is considered when the pathogen has been found to be sensitive to antibiotic treatment, which must be administered 2-3 weeks prior surgery [31], when there and good coverage of healthy soft tissues with little or moderate bone loss. Technically, the one-step revision procedure includes removing the implant and all foreign material, and replacing a new prosthesis.

 doi:10.20944/preprints202408.1663.v2

3.2.4. Rescue Operation

Unfortunately, for some patients it is not possible to perform a prosthetic re-implantation; this can lead to patient death or rescue surgeries such as arthrodesis, resection arthroplasty and amputation [32]. A rescue procedure is also to be considered in the event of failure of the revision treatment or in the case of a multi operated knee and a debilitated patient [28].

Arthrodesis

The possible indications for knee arthrodesis are: the failure of other surgical options, patients with extensive deformities, advanced alterations of the extensor mechanism, major soft tissues deficits, immunosuppression or infections with highly virulent bacteria. Arthrodesis allows to stabilize the joint, irreversibly compromising its flexion-extension, in order to allow it to be loaded and make it painless. The surgical procedure can be performed through the use of an intramedullary nail, a plate or an external fixator [28].

Arthrodesis after the removal of a total knee replacement for infection is the most common rescue procedure in the presence of a severe knee instability, however, in some cases, it may not ensure the right degree of joint stability, especially in those cases in which a constrained prosthesis has been explanted, which, for the purposes of its implant, involved a major bone resection. The success of the arthrodesis therefore also depends on the type of prosthetic implant present. Brodersen et al. (1979), out of a total of 45 cases of arthrodesis, they recorded a percentage of cessation of 81% following failure of total knee arthroplasty with condylar prosthesis, compared with a rate of 56% following failure of a constrained implant [33].

Similar results were recorded by Knutson et al. (1985); out of a total of 85 cases of arthrodesis, the success rate after removal of a semi-constrained knee prosthesis was 50%, compared with a success rate of 20% after removal of a constrained prosthesis [34,35].

Furthermore, a stable arthrodesis is even more difficult to achieve in those cases where implantation of a prosthesis has had to involve a greater bone to involve a greater bone resection, such as in the case of implantation of a mega-prosthesis (adjunt).

Resection Arthroplasty

Consists on the removal of the implant and the cement in association with a local debridement, without re-implantation of any device. The aim of this technique is to create a false joint that ensures a minimum degree of mobility. Then candidates for this type of treatment are patients with low functional demand [28].

After the resection arthroplasty, the limb is immobilized for a variable period of 3 to six months. During this time, there will be a retraction of the soft tissue at the level of the bone stumps subject to resection arthroplasty, which will ensure a certain degree of movement and stability to them.

Resection arthroplasty can provide a viable alternative to arthrodesis especially in severely disabled patients who may benefit from some degree of joint motility, especially if forced to be sedentary. In fact, a stiff knee in post-arthrodesis extension may be a factor that reduces rather than increases the chances of movement, especially in patients with severe disabilities [33].

Amputation

Represents a surgical rescue option to consider in the presence of an uncontrollable local infection despite radical attempts to eradicate the infection, an infectious state that may put seriously endangering the patient`s life, reduced bone stock and significant loss of soft tissues that do not allow the wound to close [28].

Above-knee amputation also represents a valid alternative, especially in those patients in whom the functionality of the extensor apparatus has been lost with consequent non-functionality of the joint, even if it is now restored [34].

 doi:10.20944/preprints202408.1663.v2

3.2.5. The Treatment of Surgical Wound Complications

After a knee arthroplasty operation, the presence of hemarthrosis is determined which, through the use of a drainage usually used for 24-48 hours, is reduced to a minimum. The presence of persistent bleeding inside the joint can be a factor promoting bacterial growth. If bleeding is excessive, it can lead to dehiscence of the surgical wound.

Rest and suspension of rehabilitation therapy can lead to a reduction in stress on the surgical wound and must therefore be taken into consideration in the presence of possible complications of the wound.

After a knee arthroplasty, any solution of continuity of the skin in correspondence with the surgical wound can represent a predictive alarm bell of a potentially dangerous situation for the success of the surgery.

Surgical wound healing can be affected by a number of patient-related factors, such as their nutritional status, pre-existing vascular disease, the presence of rheumatoid arthritis and / or diabetes mellitus, smoking, and previous complications or delays in wound healing.

In case of superficial dehiscence of the surgical wound after a total knee arthroplasty and in the absence of local signs and laboratory indexes of infection, the constant dressing of the surgical wound and its constant monitoring, can represent the right measures to ensure healing of the continuity of the surgical wound by secondary intention.

Much more serious is the presence of a large ischemic area around the surgical wound that can predict full-thickness tissue loss.

A decision must be made whether to surgically remove this area and then cover it with a skin graft, muscle or both.

Timing is crucial in making this decision. A surgery as early as possible ensures a greater chance of healing without further complications, first and foremost the infectious one [34].

4. Conclusions

The identification of patient's risk factors, an adequate preoperative planning and a correct surgical execution, especially in patients already operated, an antibiotic prophylaxis and finally an early management of complications can reduce the infectious risk.

In the presence of signs and symptoms and/or laboratory test suggestive of infection, early diagnosis and aggressive treatment can make the eradication of the infection.

The most important factors to be considered when choosing the best protocol for treating a knee replacement infection include:

1. The time between surgery and the development of the infection;
2. The radiographic findings and if the bone-cement and bone-prosthesis interface is involved in the infectious process and whether the prosthesis has any mobilization findings;
3. The nature of the patient's symptoms;
4. The etiological agents involved and their sensitivity to antibiotics;
5. If replanting is possible;
6. What type of prosthesis is present and how much bone loss may be present at the time of its removal;
7. The presence of complications affecting the surgical wound and / or soft tissue;
8. The functional needs of the patient.

Considering all of this, a rational management plan can usually be found with the most appropriate treatment. Early diagnosis of the infection can ensure a less invasive surgical management; in this case, surgical debridement in association with antibiotic therapy can ensure the implant retention, especially in the presence of a low virulence infectious agent.

When these criteria is absent, the prosthesis must be removed and after debridement and local antibiotic therapy, the implant must be replaced. When the infection cannot be controlled or in

 doi:10.20944/preprints202408.1663.v2

presence of an important skin and soft tissues loss, arthrodesis may be the best approach. Resection arthroplasty and amputation are reserved when neither reimplantation nor arthrodesis is possible.

Conflicts of Interest: The authors declare no conflict of interest.

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