Periprosthetic Knee Infection – Part 1: Risk Factors, Classification and Diagnosis

Infecção periprotética do joelho – Parte 1: Fatores de risco, classificação e diagnóstico

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Abstract

Infection is one of the most feared complications in the postoperative period of knee arthroplasties. With the progressive aging of the population and the increased incidence of degenerative joint diseases, there is an exponential increase in the number of arthroplasties performed and, consequently, in the number of postoperative infections. The diagnosis of these should follow a hierarchical protocol, with well-defined criteria, which lead to diagnostic conclusion, thus guiding the most appropriate treatment. The aim of the present update article is to present the main risk factors, classifications and, mainly, to guide diagnostic investigation in an organized manner.

Keywords
- arthroplasty, replacement, knee
- surgical site infection
- risk factors
- diagnosis

Resumo

A infecção é uma das complicações mais temidas no pós-operatório de artroplastias do joelho. Com o envelhecimento populacional progressivo e o aumento da incidência de doenças degenerativas articulares, observa-se um aumento exponencial do número de artroplastias realizadas e, consequentemente, do número de infecções pós-operatórias. O diagnóstico destas devem seguir um protocolo hierarquizado, com critérios bem definidos, que conduzam à conclusão diagnóstica, orientando, assim, o tratamento mais adequado. O objetivo do presente artigo de atualização é apresentar os principais fatores de risco, as classificações e, principalmente, guiar de forma organizada a investigação diagnóstica.

Palavras-chave
- artroplastia do joelho
- infecção de sítio cirúrgico
- fatores de risco
- diagnóstico

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Introduction

In the last 20 years, the longevity of the world population has been increasing in developed and developing countries. This fact increases the incidence and prevalence of degenerative diseases in general, including joint diseases.[1,2] Thus, it is natural and expected an increasing number of primary arthroplasties and revisions[3] performed as treatment of these diseases.[3–5]

The socioeconomic impact on health systems is significant, particularly in the treatment of possible infections.[6–8]

The incidence of periprosthetic knee infections in 2001 was of 2.09% and, in 2009, it was of 2.18%, with an increasing trend.[7] This complication is one of the main causes of rehospitalization,[9] accounting for between 13 and 25% of the reviews performed.[3,5,10] The estimated cost of treating periprosthetic infection is between 3 and 4 times higher than that of primary arthroplasty.[9,11,12]

The objective of the present work is to review the most current information on the prevention, diagnosis and treatment of periprosthetic knee infection.

Risk Factors

Risk factors for periprosthetic infection may be modifiable or nonmodifiable (►**Figure 1**).[13]

The modifiable factors most constantly found in literature and clinical practice are rheumatoid arthritis, diabetes mellitus, obesity (body mass index [BMI] > 30), corticosteroid therapy, alcoholism, smoking, and malnutrition, with hypoalbuminemia as reference.[14–21]

Modifiable Patient Factors	Factors with Limited Evidence of Association with ISC/IAP
* BMI – Strong	* Age (as continuous exposure) – Limited
* Smoking - Strong	* Hispanic ethnicity – Limited
* Alcohol abuse – Strong	* Native Americans and Eskimo Ethnicity – Limited
* Low income – Strong	* Asian breed – Limited
* Malnutrition (hypoalbuminemia) – Source	* History of drug abuse – Limited
* History of DM – Strong	* Rural x non-rural domicile - Limited
* History of CVD – Moderate	* Under body weight – Limited
* History of ICC – Strong	* History of hypertension – Limited
* History of cardiac arrhythmia – Strong	* History of osteoarthritis – Limited
* DVP Story – Strong	* History of post-traumatic arthritis – Limited
* Chronic lung disease – Strong	* Low and high risk dental procedures – Limited
* Chronic obstructive pulmonary disease – Strong	* History of UTI – Limited
* History of kidney disease – Strong	* History of dementia – Limited
* History of liver disease/cirrhosis – Strong	* Hypercholesterolemia – Limited
* AR History – Strong	* Ulcerative peptic disease – Limited
* History of cancer/malignancy – Strong	* Valvular disease – Limited
* History of osteonecrosis – Strong	* Metastatic tumor – Limited
* History of depression – Strong	* History of coagulopathy – Limited
* History of psychosis – Strong	* History of venous thromboembolism – Limited
* History of HIV/AIDS – Strong	* Pulmonary circulation disorders – Limited
* Neurological disease (hemiplegia, paraplegia) – Moderate	* Hypothyroidism – Limited
* History of corticosteroid use – Strong	* Hepatitis (B or C) – Limited
* History of intra-articular corticosteroid injection – Moderate	* Hydroelectrolyte imbalance - Limited
* Prior joint surgery – Moderate	* Autologous blood transfusion – Limited
* Revision arthroplasty – Strong	
* Previous joint infection – Moderate	
* Fragility – Moderate	
* Preoperative anemia – Strong	
* ASA grade >2 – Strong	
* Elevated Charlston Comorbidity Index – Strong	
* Preoperative hyperglycemia and elevated HbA1C – Moderate	
* Allogeneic blood transfusion – Strong	
* Warfarin / LMWH prophylaxis – Moderate	

Non-Modifiable Patient Factors
* Age (> 75 years) – Moderate
* Male – Strong
* Black race – Strong
* TKA vs THA – Strong

Fig. 1 Risk factors for periprosthetic infection - reproduction of the International Consensus on Musculoskeletal Infections 2018 (ICM-2018).[13]

Table 1 McPherson classification for periprosthetic infection

Factor	Degree	Description
Type	I	Acute infection (< 4 weeks postoperatively)
	II	Acute hematogenous infection (< 4 weeks of symptoms)
	III	Chronic infection (> 4 weeks of symptoms)
Host factors (comorbidities and immunity)	A	Not compromised
	B	Compromised (1–2 comorbidity factors)
	C	Very compromised (> 2 comorbidity factors) or one of the factors below: ◦ Neutrophil count < 1,000 ◦ CD4 count < 100 ◦ Intravenous drug user ◦ Active infection elsewhere ◦ Tumor or dysplasia of the immune system
Local Factors	1	Not compromised
	2	Compromised (1–2 comorbidity factors)
	3	Very compromised (> 2 comorbidity factors)

Systemic and local factors are described in ►**Table 2**.

Some other clinical and social conditions are also described as associated with a higher rate of periprosthetic infection (PPI), such as preoperative American Society of Anesthesiologists (ASA) classification > 2, low income, peripheral vascular disease and others listed in ►**Table 1**.[14,21,22]

Active skin lesions, either near the site or at a distance, have a potentially increased risk of periprosthetic articular infection, as well as surgery or previous joint infection.[16,20,23]

Some studies report an increased rate of infection in total knee arthroplasty (TKA) by post-traumatic arthrosis, mainly with previous surgery and retained implants.[24,25]

Bergen et al.[26] found in a comparative retrospective cohort (109 patients with implants and 109 patients without) an increase in the infection rate in patients undergoing TKA with knee implant (osteosynthesis or osteotomies). However, there was no difference when comparing the groups with previous removal of the implants ($n = 43$) with those removed during the TKA procedure ($n = 46$).

There is controversy regarding the increase rate of infection after TKA in patients undergoing previous joint infiltration. Some studies have shown an increased risk of infection when TKA is performed up to 3 months after joint infiltration.[27,28] On the other hand, other studies did not find significant differences, even in short periods after infiltration (10 weeks)[29] or in patients submitted to multiple infiltrations.[30] The II-ICM-2018 (II International Consensus on Muscleskeletal Infection – 2018) suggests waiting at least 3 months after infiltration to perform arthroplasty.[31]

Regarding the nonmodifiable factors, age alone does not seem to be a predisposing factor for infection.[15,16] Regarding gender, some studies show a higher infection rate in men than in women[15,16] Afro descendants also have higher percentage of infection when compared with Caucasians.[21]

Komnos et al.[32] retrospectively evaluated patients with arthroplasties in more than one joint. In this study, they concluded that periprosthetic infection of a joint may predispose to hematogenous infection in another prosthetic site. The risk situations for this complication are: female gender, rheumatoid arthritis, Methicillin-Resistant Staphylococcus aureus (MRSA) infection and patients with fever at the time of diagnosis of the first infected joint.

Classification

Classifications are important to stratify and guide management in various clinical conditions, as well as to standardize communication between colleagues.[33]

Segawa et al.,[34] in 1999, published a retrospective study proposing a classification and its respective treatment based on the chronology of the infection and its etiology, dividing periprosthetic infections into: positive cultures in revision perioperative harvest, acute superficial infection, acute deep infection, chronic infection, and acute hematogenous infection. However, the classification does not consider the conditions of the patient, local and systemic, or the etiological agent.[33]

McPherson et al.[35,36] described a classification system for hip and knee periprosthetic infection based on a retrospective analysis of cases evaluating three factors: type of infection (acute, acute or chronic hematogenous), host factors, and local factors (►**Table 2**). This classification was validated by the International Consensus on Musculoskeletal Infection with moderate evidence index and 74% of panel agreement.[37]

Alt et al.[38] proposed a new classification based on the TNM classification for tumors, adapting it to periprosthetic infection, which emphasizes the pathogenicity of the etiological agent.

In the proposed classification, "T" would be tissue evaluation, "N," non-human cellular factor (etiological agent), and "M", host morbidity, according to the Charlson comorbidities classification (►**Figure 2**).[38–40]

Table 2 Local and systemic factors for the McPherson classification

Factor	Description
Systemic host involvement (comorbidity or immunity)	Age >80 years old
	Alcoholism
	Dermatitis or active chronic cellulitis
	Permanent catheter
	Chronic malnutrition (albumin < 3.0 g/dL)
	Chronic nicotine use (inhaled or oral)
	Diabetes mellitus (requiring drug treatment)
	Liver failure (cirrhosis)
	Use of immunosuppressive drugs (corticosteroids, methotrexate, cyclosporine)
	Malignancy (active or history)
	Pulmonary insufficiency (SaO2 < 60% in room air)
	Chronic renal failure on dialysis
	Systemic inflammatory disease (Rheumatoid Arthritis, Systemic Lupus Erythematosus)
	Systemic immune impairment by infection or immunodeficiency (AIDS, acquired immunodeficiencies)
Involvement of the affected limb (wound and limb conditions)	Active infection (> 3–4 months)
	Multiple incisions – skin bridges
	Loss of soft tissue due to previous trauma
	Subcutaneous abscess (extension > 8 cm^2)
	Cutaneous synovial fistula
	Previous periarticular fracture or previous joint trauma (crushing)
	Previous local irradiation
	Peripheral vascular insufficiency – arterial or venous

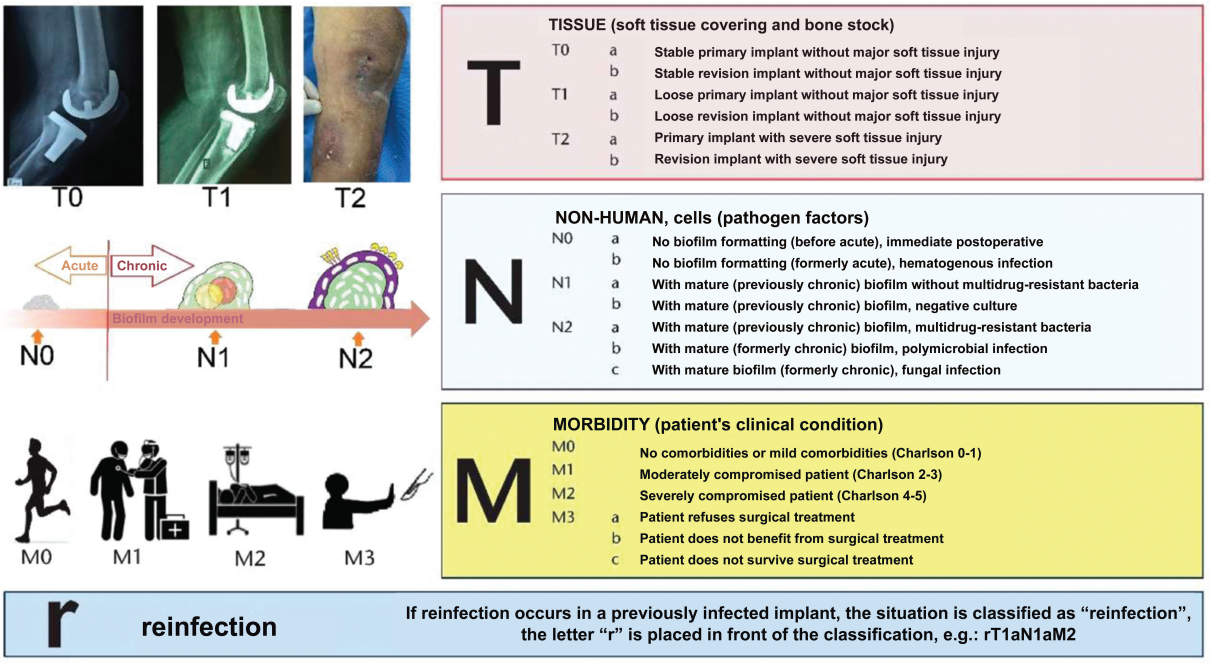

Fig. 2 TNM classification for PPI.[40]

The idea of classifying these three factors seems the most appropriate approach; however, we did not find any studies validating this classification.

Diagnosis

The diagnosis of post knee arthroplasty infection has been a challenge. In the first weeks postoperatively, the occurrence of pain, local heat, and functional disability may be normal and not related to any type of bacterial infection.

Thus, it is essential to define reproducible and objective criteria that charaterize the presence of infection.

Following the concept that the diagnosis of infection is often a multifactorial analysis - clinical, laboratory, imaging data and synovial fluid analysis - it is very important to hierarchize the actions in order to build this same diagnosis within a logical and progressive clinical reasoning.

We consider the strategy defined by ICM-2018 the most appropriate research option. In addition to guiding the researcher to the next step towards the diagnostic's conclusion, it brings scientific knowledge of better available evidence and the experience of hundreds of orthopedists, infectologists and microbiologists around the world. The proposed algorithm was tested and validated, presenting high sensitivity (96.9%) and specificity (99.5%) rates.[37,41]

Following this criterion, the diagnosis of infection is defined by the presence of one of the so-called major criteria – fistula with joint communication or two positive cultures for the same microorganism identified using culture media – or by scoring clinical, serum or scoring from analysis of the synovial fluid obtained by joint puncture (►**Figure 3**).[37]

The occurrence of fistula is found in ~ 13% of cases.[38] In its absence, when the patient presents with pain in the operated knee, heat and, often, decreased range of motion, it is imperative to request blood tests for evaluation of the white series, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (PCR), and D-dimer.[37]

ESR and PCR are inflammatory markers used as the first line in the screening of patients with suspected infection, with a sensitivity of ~75 88% and a specificity of 70 74%, respectively.[42] The sensitivity of both combined ranges from 84 to 86%, and the specificity from 47 to 72.3%.[43,44] C-reactive protein reaches its highest value on the 3rd postoperative day and remains above normal for ~ ≥ 3 weeks.[45] VHS remains elevated for at least 6 weeks.[46] Noting that, in patients with inflammatory arthritis, the cutoff value of these markers may be higher due to the influence of the underlying disease,[47] just as the use of antibiotics can generate false-negatives.[48] A recent study showed greater sensitivity (89%) and specificity (93%) for D-dimer in relation to traditional ESR and PCR.[43]

Major Criteria (at least one of the following)	Decision
Two positive cultures of the same organism using standard culture methods	Infected
Fistula with evidence of communication with the joint or visualization of the prosthesis	

Minor Criteria	Threshold		Punctuation	Decision
	Acute€	Cronic		
Serum CRP (mg/L) Or D-Dimer (ug/L)	100 Unknown	10 860	2	Sum of pre- and post-operative points: ≥ 6 infected 3 to 5 inconclusive* < 3 not infected
ESR elevation (mm/hr)	Not important	30	1	
Elevated synovial leukocytes (cells/µL) *Or* Leukocyte Esterase *Or* Alpha-defensin (qualitative / quantitative)	10.000 ++ 1.0	3.000 ++ 1.0	3	
Elevated Synovial PMN (%)	90	70	2	
Only Positive Culture			2	
Positive Histology			3	
Positive Intraoperative PurulenceV			3	

€ This criterion has never been validated in acute infections. V No role in suspected local adverse tissue reaction.
* Consider more molecular diagnostics with next-generation sequencing.

Fig. 3 Diagnostic criteria of the Musculoskeletal Infection Society (CIIM reproduction).

Another study observed a decline in basal D-dimer levels on the second postoperative day.[46]It is important to note that ~ 2.5% of the infections do not present alterations in the aforementioned tests.[37]

The next step following the investigation is arthrocentesis, sending the synovial fluid for laboratory analysis of cellularity (cytometry) and culture/antibiogram. There is no formal contraindication to joint aspiration.[37,49] In this procedure, which concludes the diagnosis in 65% of the cases, it is essential that the criteria of maximum barrier to contamination are met, performed by an experienced professional with adequatev packaging, and immediate shipment of the material to the laboratory.[37]

In the acute phase, the presence in the synovial fluid of $\geq$ 10,000 leukocytes/μL, with at least 90% polymorphonuclear (PMN), and $\geq$ 3,000 leukocytes/μL in the chronic phase, with at least 70% PMN, indicate infection.[37]

As for the culture of the aspirated liquid, some criteria should be followed to minimize the risk of false-negative. It is important to perform a prolonged time of culture, since most of the negative samples are infections by bacteria of time-consuming growth, interrupted before the appropriate time.[50]

The collected joint fluid can also be used for 2 other tests: alpha-defensin and leukocyte esterase.[37]

Alpha-defensin is an antimicrobial peptide produced by neutrophils in response to pathogens.[37,51,52] This marker can be researched in the synovial fluid by laboratory immunoassay or by the lateral flow test, which is a rapid test with a specific kit that can be performed in the operating room with results in a few minutes. The lateral flow test presents a sensitivity rate of 78.5% and a specificity rate of 93.3%, according to a systematic review conducted by the CIIM-2018 with grouped data from 486 patients.[41] Immunoassay has a sensitivity rate of 98.1% and a specificity rate of 96.4%.[54] Alpha-defensin is not influenced by recent antibiotic use, traces of blood in the sample, or comorbidities such as inflammatory diseases. The rapid test requires a small volume of synovial fluid (15 μL), which can be a great advantage in cases of absence of joint effusion.[53,54] On the other hand, in the presence of metallomy, it may present false-negative in up to 30% of cases; it can also be influenced by crystal arthropathy (gout) and should not be done in hematoma aspirate.[53]

Leukocyte esterase is a test with a sensitivity of 85.7% and a specificity of 94.4% according to the systematic review conducted by the CIIM-2018 with grouped data from 2,061 patients.[41] This test is also not influenced by recent antibiotic use, but the presence of blood in the sample alters the readability of the test, and centrifugation may be necessary to neutralize erythrocyte interference.[37,56]

In cases in which it is not possible to aspirate enough content for analysis (dry puncture) or whose cultures are negative, which correspond to ~ 17% of cases, intraoperative findings of pus, histological analysis, tissue culture, and new generation sequencing may help in the diagnosis of infection.[41] It is not appropriate to perform joint washing in cases of dry puncture.[41]

Even with the entire arsenal of tests and the algorithm structured and validated, in ~ 5% of cases the diagnosis of infection cannot be confirmed.[41]

Some imaging tests may help in the planning of treatment but have low specificity regarding diagnosis.[57] Signs of early release on conventional radiography lead to suspected infection.[58] Computed tomography (CT) (especially arthrotomography) and magnetic resonance imaging (MRI) with metal suppression may also show signs of loosening, bone defects and, occasionally, osteomyelitis;[57] however, due to their high cost and low specificity, these tests are not recommended as diagnostic measures.[58,59]

On the other hand, other tests have been used to differentiate aseptic loosening from infection, especially in cases of dry puncture, such as the combination of scintigraphy with marked leukocytes and single photon emission computed tomography (SPECT-CT), which also has the advantage of showing the extent of infection impairment, both in bone and soft tissue, and may be of great value in the planning of surgery.[57]

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