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Review

Diagnosis of periprosthetic hip infection: a clinical update

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Abstract. Periprosthetic joint infection (PJI) is a serious complication following hip arthroplasty, which is associated with significant health cost, morbidity and mortality. There is currently no consensus in the optimal definition of PJI, and establishing diagnosis is challenging because of conflicting guidelines, numerous tests, and limited evidence, with no single test providing a sensitivity and specificity of 100%. Consequently, the diagnosis of PJI is based on a combination of clinical data, laboratory results from peripheral blood and synovial fluid, microbiological culture, histological evaluation of periprosthetic tissue, radiological investigations, and intraoperative findings. Usually, a sinus tract communicating with the prosthesis and two positive cultures for the same pathogen were regarded as major criteria for the diagnosis, but, in recent years, the availability of new serum and synovial biomarkers as well as molecular methods have shown encouraging results. Culture-negative PJI occurs in 5-12% of cases and is caused by low-grade infection as well as by previous or concomitant antibiotic therapy. Unfortunately, delay in diagnosis of PJI is associated with poorer outcomes. In this article, the current knowledge in epidemiology, pathogenesis, classification, and diagnosis of prosthetic hip infections is reviewed. (www.actabiomedica.it)

Key words: Prosthetic joint infection, hip arthroplasty, biomarkers, microbiology, diagnosis

1. Introduction

Periprosthetic hip infection (hereinafter referred to as PJI) is one of the most feared complications of total hip replacement (THR), that occurs in 0.3-2.9% of primary and in 2.1-15.3% of revision arthroplasties (1, 2). The absolute incidence is expected to growth due to the increasing number of primary THR (1). To date, infection is the third leading cause for hip revision surgery (1). Moreover, PJI increases patient's morbidity, hospitalization time and mortality, as well as heath care cost. The cost of treatment of a PJI is 2.8 and 4 times than an aseptic revision and primary THR, respectively (3). The lack of consensus in the optimal definition, conflicting guidelines, and numerous tests (none providing a sensitivity and specificity of 100%), make the diagnosis extremely challenging (4).

2. Pathogenesis and role of biofilm

Historical rates of PJI showed a higher risk period during the first 2 years after surgery, and 60-70% are caused by intraoperative inoculation (5). The second most frequent mode of infection is the hematogenous spread from a distant focus (5, 6). According to Rakow et al., only 68% have a known origin, and typically are from skin and soft tissue, heart valve and urinary tract (7). The last pathway of infection is the direct contact or contiguous spread from an adjacent site.

Biofilm is a complex community of microorganisms embedded within an extracellular matrix that forms on surfaces of prosthesis. The role of biofilm is to create a closed and inaccessible microenvironment to the immune response of the host and the antibiotic therapy. Moreover, biofilm reduces the metabolism

and the growth rate of microorganisms, making them difficult to isolate (8). The bacterium adheres to the foreign body material of orthopaedic implants, and the greatest level of adherence was observed on highly crosslinked polyethylene (9). Biofilm is already present 36 hours after bacterial adhesion with complete maturation at 3-4 weeks (8). This period is crucial to distinguish between acute and chronic PJIs.

3. Classification

Over the years, several classification systems of PJI have been proposed, which are based on time of onset of symptoms, time elapsed from surgery, and grade of maturation of biofilm. The Tsukayama classification is the most frequently used, including the time of presentation and onset of symptoms after the initial surgery (10) (Table 1).

Time of occurrence is associated with significant differences in the etiological agent, since more virulent microbes, such as S. aureus, tend to cause earlier infections, whereas more indolent agents, such as coagulase-negative Staphylococci or Cutibacterium acnes, account for delayed infections. Trampuz and Zimmerli classified PJI into acute and chronic according to the pathogenesis, time of onset of symptoms, biofilm maturity, and causative microorganism (11) (Table 2).

4. Etiology

Microbiologic diagnosis in PJI is crucial to provide the best treatment strategy. Many bacterial pathogens have been implicated. S. aureus and coagulase-negative staphylococci are the most common reported agents, and are responsible for nearly 60% of early cases (5). Polymicrobial infections have been reported in 9% to 40% of PJIs, and are more common in the first postoperative period (10, 12). Delayed infections are usually caused by low-virulent agents, such as coagulase-negative staphylococci and Enterococcus spp., whereas late infections from hematogenous origin are more commonly due to S. aureus (5).

Table 1. Tsukayama classification of PJI.

Infection type	**I: Early postoperative infection**	**II: Late chronic infection**	**III: Acute haematogenous infection**	**IV: Positive intraoperative culture**
Onset of symptoms after surgery	Up to 4 weeks	After 4 weeks	After an asymptomatic period	-
Pathogenesis	Exogenous	Exogenous or hematogenic	Hematogenic	-
Clinical features	Fever, inflammatory signs, prolonged wound drainage	Fever, sinus tract, local edema, pus accumulation	Fever, inflammatory signs, bacteraemia	Painful arthroplasty

Table 2. Classification of PJI into acute and chronic infection.

Type of PJI	**Acute PJI**	**Chronic PJI**
Pathogenesis: • Perioperative • Haematogenous	Early postoperative: < 4 weeks after surgery < 3 weeks of symptoms	Delayed postoperative: ≥ 4 weeks after surgery ≥ 3 weeks of symptoms
Biofilm maturity	Immature	Mature
Clinical features	Acute joint pain, fever, inflammatory signs	Chronic pain, loosening of the prosthesis, sinus tract
Causative microorganism	High-virulent: *Staphylococcus aureus*, gram-negative bacteria (e.g. *Escherichia coli*, Klebsiella spp., *Pseudomonas aeruginosa*)	Low-virulent: coagulase-negative Staphylococci (e.g. *Staphylococcus epidermidis*), *Propionibacterium acne*s

5. Diagnosis

In the last decade, no less than 7 different definitions have been proposed by independent societies, based on a multimodal and combined approach of clinical data and diagnostic test (13-19) (Table 3). The lack of consensus on the diagnostic definition of PJI is due to the absence of a test with a specificity and a sensibility of 100%. To date, the lack of a single reference test, the discordance about the diagnostic accuracy, and the threshold value of the current tools, as well as the difficulty in the diagnosis of low-grade infections, are current diagnostic problems.

6. Diagnostic categories

6.1. Clinical features

Clinical presentation relates to the pathogenesis, time of onset from implantation, virulence of the pathogen, and host immune response (5, 19, 20). The presence of open wound, sinus tract, or abscess, is more common in patients with contiguous or perioperatively acquired PJI. Conversely, systemic signs or symptoms, such as fever or chills, usually occur in patients with hematogenous infection (5). While fever, chills and joint erythema are highly specific, they are also insensitive for diagnosing (21). A sinus tract communicating with the joint or an exposed implant are the only fully specific findings, but present a low sensitivity (20-30%) (13, 14, 16-19). Pain and joint stiffness are the most sensitive clinical features, but they are also common in aseptic failures (21). Specifically, joint pain at rest is the most frequently reported symptom, but its specificity is low (28.3%) (5). History of postoperative wound healing complications, such as prolonged leakage or dehiscence, and hematoma or superficial infection after implantation, or a recent bacteremia are highly suspicious (22). The time of failure is a relevant information to consider. Early loosening (< 5 years after surgery) is more often caused by hidden PJI than late loosening (19). Intraoperative finding of purulence around a prosthesis is poorly correlated with isolation of a microorganism from culture, with a diagnostic accuracy of 77% (23). It is difficult to distinguish between pus and other turbid fluids, which can be formed in adverse local tissue reaction (ALTR), metallosis, aseptic loosening, inflammatory arthropathy, and crystal-induced arthritis.

6.2. Serum biomarkers

Numerous studies have investigated serum biomarkers and their role in diagnosing PJI. One of the major pitfalls is that they are not specific, and can be elevated due to concurrent infection, autoimmune disorder, metallosis, gout or other crystal arthropathy, inflammatory joint disease, periprosthetic fracture, and during the early postoperative period. These biomarkers may also be normal in low-grade infections (6, 24, 25).

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ESR and CRP are the first-line screening tests in PJI as widely available and inexpensive (2, 26). Thresholds of > 30 mm/hour for ESR and > 10 mg/L for CRP have been proposed for detecting chronic infection, and a cut-off > 100 mg/L for CRP for acute manifestations has been hypothesized (13-15, 17, 19). Generally, CRP increases rapidly after surgery and peaks at the second-third postoperative day, dropping gradually to initial values on day 21, even if it can be elevated up to three months after the index procedure (27). At a cut-off value of 10 mg/L, CRP shows a sensitivity and a specificity ranging from 68% to 89.9% and from 71% to 80%, respectively (20, 28, 29). ESR peaks on day 5 after operation, dropping close to index values at the end of the third month (27). Sensitivity and specificity of ESR ranges from 42% to 94% and 33% to 87%, respectively (26). ESR and CRP have high sensitivity, but their major drawback is the limited specificity. ESR is not useful in detecting acute infection, and ESR and CRP both are influenced by previous antibiotic therapy and other concomitant non-infectious causes (13, 28). It has also been demonstrated that ESR and CRP cannot be considered a screening tool for PJI or to proceed to a second stage (6, 20, 25). Perez-Prieto et al. found that one third of PJIs presented normal CRP levels and that approximately two thirds of these also had a normal ESR (20). Consequently, their negative association is not enough to exclude infection, as the false-negative rate is as high as 2.5%-5% (4, 25, 26).

Table 3. Comparison of the diagnostic criteria adopted in 7 PJI definitions published from 2011 to 2021.

	Criteria	**Scoring System**
MSIS 2011 (13)	Major: 1. Sinus tract communicating with the prosthesis 2. At least two positive cultures for the same pathogen from two separate tissue or fluid samples Minor: 1. Serum CRP >10 mg/L and ESR >30 mm/hr 2. Elevated synovial WBC count 3. Elevated PMN% 4. Purulence in the affected joint 5. Single positive culture 6. Greater than 5 PMN in 5 HPFs at the histological analysis	1 of the 2 Major Criteria OR ≥ 4 of 6 Minor Criteria
IDSA 2013 (16)	1. Sinus tract communicating with the prosthesis 2. Purulence around the prosthesis 3. Acute inflammation on histopathological examination 4. At least two positive cultures for the same pathogen OR a single positive culture with high virulent organism	≥ 1 Positive Criteria
ICM 2013 (14)	Major: the same 2 criteria proposed by MSIS 2011 Minor: 1. ESR >30 mm/hr and CRP >100 mg/L for acute infections, >10 mg/L for chronic infections 2. Synovial WBC count >10,000 cells/mL for acute infections, >3,000 for chronic infections 3. PMN% >90% for acute infections, >80% for chronic infections 4. ++ change on LE test strip 5. Single positive culture 6. Greater than 5 PMNs in 5 HPFs	1 of the 2 Major Criteria OR ≥ 3 of 5 Minor Criteria
ICM 2018 (17)	Major: the same 2 criteria proposed by MSIS 2011 Minor: 1. ESR >30 mm/hr for chronic infections (score 1) 2. CRP >100 mg/L for acute infections, >10 mg/L for chronic infections or D-Dimer >860 μg/L for chronic infections (score 2) 3. Synovial WBC count >10,000 cells/mL for acute infections, >3,000 for chronic infections (score 3) 4. PMN% >90% for acute infections, >70% for chronic infections (score 2) 5. LE ++ (score 3) 6. Positive alpha-defensin (score 3) 7. Single positive culture (score 2) 8. Positive histology (score 3) 9. Positive intraoperative purulence (score 3)	1 of the 2 Major Criteria OR Minor Criteria scoring: ≥ 6 Infected, 3-5 Possible infected ("Consider molecular diagnostics such as next-generation sequencing"), < 3 Not infected
MSIS 2018 (15)	Major: the same 2 criteria proposed by MSIS 2011 Preoperative Minor: 1. Elevated serum markers: ESR, CRP and D-Dimer 2. Elevated synovial markers: WBC count, PMN%, LE, alpha-defensin and CRP Intraoperative Minor: 1. Purulence around the implant 2. Single positive culture 3. Positive histology	1 of the 2 Major Criteria OR Preoperative or Intraoperative Minor Criteria scoring ≥ 6

WAIOT 2019 (18)	Rule OUT tests (sensitivity >90%): 1. ESR >30 mm/hr 2. CRP >10 mg/L 3. WBC count >1,500/μL 4. LE (++) 5. Alpha-defensin immunoassay (>5.2 mg/L) 6. CT bone scan Rule IN tests (specificity >90%): 1. Purulence or draining sinus or exposed joint prosthesis 2. Serum IL-6 >10 pg/mL 3. Serum PCT >0.5 ng/mL 4. Serum D-Dimer >850 ng/mL 5. Synovial WBC >3000/mL 6. LE (++) 7. Alpha-defensin 8. Positive cultural examination 9. Positive histology 10. Leukocyte scintigraphy	Number of positive rule IN tests – number of negative rule OUT tests: <0, negative microbiological and histological findings: no infection <0, negative histological findings but 1 positive culture: contamination <0, positive cultural examination and/or positive histology: biofilm-related implant malfunction ≥0, positive cultural examination and/or positive histology: low-grade PJI ≥1, positive cultural examination and/or positive histology: high-grade PJI
EBJIS 2021 (19)	1. Radiological signs of loosening within the first 5 years 2. Previous wound healing problems 3. History of recent fever or bacteraemia 4. Purulence around the prosthesis 5. Serum CRP >10 mg/L 6. WBC >1,500 cells/μL 7. PMN% >65% 8. Single positive culture 9. >1 CFU/mL at sonication 10. Presence of ≥5 neutrophils in a single HPF 11. Positive WBC scintigraphy 1. Sinus tract with evidence of communication to the joint 2. WBC >3,000 cells/ml or PMN% >80% 3. Positive alpha-defensin 4. ≥ two positive cultures with the same organism 5. > 50 CFU/mL at sonication 6. Presence of ≥5 neutrophils in ≥5 HPF	Infection likely (two positive findings) Infection confirmed (any positive findings)

Abbreviations: MSIS: Musculoskeletal Infection Society; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: synovial white blood cell count; PMN%: synovial neutrophil percentage; IDSA: Infectious Diseases Society of America; ICM: International Consensus Meeting; WAIOT: World Association against Infection in Orthopedics and Trauma; EBJIS: European Bone and Joint Infection Society; IL-6: interleukin-6; PCT: procalcitonin; LE: leukocyte esterase; HPFs: high power fields (400x);

Interleukin-6 (IL-6). In case of infection, blood levels of IL-6 increase to 30-340 pg/mL in the first 2 days, with a fast return to normal values (< 1 pg/mL) 3-5 days after surgery (5). Therefore, it is considered an early indicator of PJI. Overall, sensitivity and specificity of serum IL-6 test range from 47% to 99% and 76.79% to 95%, respectively (24, 26). Currently, several cut-offs have been proposed, but the high cost and the limited number of studies restrict its use.

Procalcitonin (PCT). At levels > 0.3 ng/mL, PCT shows a specificity ranging from 89% to 98%, but sensitivity is low (33-58%) (24, 26, 30). Consequently, PCT is not recommended for use as a rule-out diagnostic tool for PJI.

White blood cell (WBC) count, polymorphonuclear (PMN) % and tumor necrosis factor-α (TNF-α). Despite a quite high specificity (range 85-89%), serum WBC count and PMN% show a very low sensitivity (41-49%), while TNF-α at a cut-off level of 40 ng/mL shows a sensitivity of 43% and a specificity of 94% (24). To date, these biomarkers are not recommended to detect infection (24, 30).

D-dimer. In recent years, serum D-dimer has become a promising new marker for the diagnosis of PJI. Shahi et al. reported that serum D-dimer outperformed both ESR and CRP, with a sensitivity of 89% and a specificity of 93% at a threshold level of 860 ng/mL (31). Serum D-dimer rapidly increases and returns to normal values at the second postoperative day, before reaching a second peak at postoperative week two[32]. The reported sensitivity and specificity range from 87.5% to 89.5% and from 89% to 93%, respectively (26, 32). The more rapid rise and fall of D-dimer in the early postoperative period and its widely availability make this marker a useful tool to the currently available laboratory infection exams. However, further studies are required to reproduce its reliability.

6.3. Synovial biomarkers

Preoperative joint aspiration is the most valuable diagnostic tool that should be performed for every painful prosthetic joint prior to revision (5, 26). There are no absolute contraindications to arthrocentesis, as the use of anticoagulant drugs showed no statistical difference in terms of infection and bleeding rate (26). Antibiotic therapy should be discontinued at least two weeks before the procedure in order to increase sensitivity. Dry tap occurs in 23-32% of cases, and assisted ultrasound-guided aspiration should be considered, as injection of normal saline or local anesthetics increases the rate of false negative results (33). To date, synovial biomarkers have become the cornerstone of diagnostic algorithms to confirm or exclude PJI. However, these markers should be interpreted with caution in case of gout, crystal and inflammatory arthritis, periprosthetic fracture, dislocation and instability, and even in the early postoperative time.

WBC count and PMN%. Different cut-offs for synovial WBC counts and PMN% have been proposed. However, there is a high level of consensus supporting a value of 3000 cells/μL for WBC and a percentage of PMNs >80% to confirm a chronic PJI, whereas in acute infection a threshold of WBC >10000 cells/μL and a percentage of PMN >90% are recommended (13-15, 17). The sensitivity ranges from 36% to 94% for leukocyte count, and from 77% to 97% for PMN%, while specificity varies from 80.8% to 98% for both (24, 26, 28). Synovial fluid cells may be elevated in hemarthrosis, periprosthetic fractures, dislocation, metallosis, in the early postoperative period (within the first 6 weeks) and in inflammatory arthropathy. However, Cipriano et al. stated that WBC count and PMN% might perform similarly in patients with and without inflammatory arthritis (34). Furthermore, prior antibiotic therapy is associated with high rate of false negative results (4).

Alpha-defensin. Alpha-defensin is an antimicrobial protein that can be measured by the Alpha Defensin Lateral Flow (ADLF) test, which qualitatively determines the presence in synovial fluid within 10-20 minutes, or by the Enzyme-Linked Immunosorbent Assay (ELISA), which is a quantitative method for the detection of alpha-defensin within 24 hours. The ADLF test shows a lower sensitivity (43-97%) compared to the ELISA test (92-100%), but both present a high specificity ranging from 93% to 100% (24, 26, 35-37). Non-infectious inflammatory conditions, such as metallosis, ALTR, crystal arthropathy and inflammatory diseases, might result in false-positive results (35). Although this synovial biomarker is not suitable for screening of PJI due to its low sensitivity, it can be used as a confirmatory test in case of doubt (26, 29, 36). In the early postoperative period, as well as during antibiotic therapy and in low grade infections, alpha-defensin can be used with a high specificity (29, 36). However, alpha-defensin testing is expensive and not widely available, and consequently its current cost does not compensate the advantages in the diagnosis of PJI compared with other methods (29, 37, 38).

Leukocyte Esterase (LE). Colorimetric reagent strip tests are increasingly being used to detect LE activity in suspected PJI. It is a simple, low cost and quick method, that could be used intraoperatively (26,29, 39). A "++" reading provides 81-93% sensitivity and 97-100% specificity; a "+" reading gives 96-97% sensitivity and 84-96% specificity (24, 26, 29, 37). According to its high specificity, LE strips serve as a reliable option for a secondary confirmatory rule-in test (40). However, this test is influenced by the presence of red blood cells in the synovial fluid, as it interferes with the colour reading of the strips (40). In these cases, centrifugation of the sample is recommended (39). As alpha-defensin, leukocyte esterase is also valid

during antibiotic therapy, and even for metal-on-metal implants (41). Several authors reported the same diagnostic accuracy for LE and alpha-defensin (28, 37).

Synovial CRP and IL-6. Synovial CRP seems to perform better than serum CRP, with a reported mean sensitivity of 85-92% and specificity of 71-98% (24, 29). Also synovial IL-6 level has been shown to be more specific than serum amount (24). At threshold > 2100 pg/mL, the sensitivity and specificity are 62.5-100% and 85.7-100%, respectively (2, 30, 42). Additional studies are required to validate the role of these biomarkers.

6.4. Histopathology

Histopathological evaluation demonstrating acute inflammation is suggestive of PJI. The histological criteria of acute inflammation include 1 to 10 neutrophils per high-powered field (HPF) at a magnification of 400 (5, 11, 43, 44). The most used definition is the presence of at least 5 neutrophils per HPF in at least 5 separate microscopic fields (13-15). Sensitivity and specificity of histopathological analysis range from 59.7% to 95% and 88% to 100%, respectively (24, 38). This examination is not likely to be affected by preoperative antibiotics, and results are available intraoperatively with the use of frozen-section analysis. However, it has been reported that some pathogens, such as P. acnes and coagulase-negative staphylococci, may not consistently elicit a robust neutrophilic inflammatory response, reducing the sensitivity of the examination (45).

The basis of pathological evaluation of PJI involves tissue sampling of the areas adjacent to the prosthesis which appear to be infected upon gross intraoperative inspection. Several anatomical sites for operative periprosthetic tissue biopsy have been traditionally used. Bori et al. stated that the periprosthetic interface membrane was the most accurate site for histological diagnosis of PJI, with sensitivity of 83%, greatly than that for the pseudocapsule (42%) (46).

6.5. Microbiology

Identification of the infectious microorganism is the most important goal. At least 3 to 6 deep intraoperative samples (periprosthetic tissue and synovial fluid) should be submitted for the culture (5,6,11,47). The number of tissue samples collected depends on the grade of infection. Samples should be retrieved from the areas where signs of infection are more evident and from different parts of the surgical fields (6). Prior to collecting microbiological samples, any antibiotic therapy should be discontinued for 2 weeks (2, 6, 47), although perioperative prophylactic antibiotics prior to sampling for culture remain controversial. Two samples must be collected from the same site, one for histopathological analysis and one for microbiological examination in order to have a correlation between them. The lack of standardization of collection, packaging, transport, and method techniques represents a challenge for traditional cultures. Sterile certified and hermetically sealed containers should be used, along with separate surgical instruments to avoid a risk of cross-contamination (6, 48). The laboratory transport should occur as soon as possible to avoid bacterial killing, that has been proven after 6 hours of sampling.

Swab cultures have a lower sensitivity and specificity compared with tissue cultures, and are not recommended due to the high risk of contamination and false positive results (6, 11, 49). Sensitivity of intraoperative swabs is lower than that of intraoperative samples (70% vs 93%), as well as the specificity (89% vs 98%) (49). Moreover, swabs of superficial wounds or sinus tracts can mislead by detecting the colonizing rather than the infecting microorganisms (6). Tetreault et al. showed that the correlation between swab of superficial sinus tract and intraoperative sample was only 53% (50).

Microbiological analysis could be performed on preoperative synovial fluid aspiration, intraoperative tissue/liquid samples, or sonication of removed implants. The sensitivity of preoperative synovial fluid culture in chronic infections is low and ranges from 45% to 75%, while specificity ranges from 88% to 97%, making this exam not useful as screening test to rule out PJI (6, 24, 33, 38). Intraoperative sample analysis have higher values of sensitivity and specificity compared to preoperative aspiration ones (45%-94% and 91%-98%, respectively) (11, 24, 51). The optimal incubation time is controversial and ranges from up to 4 days for aerobics, up to 7 days for anaerobics, to at least 14 days for low-virulent organisms. Some authors

advocate for extended incubation to increase sensitivity as incubation time for at least 14 days is especially important for anaerobic pathogens, improving recovery of P. acnes and other low virulent organisms (26). One concern about prolonging incubation time is the potential of increasing the number of contaminants. However, Schafer et al. reported that 52% of contaminants were growing within the first 7 days of incubation (52).

Infection is confirmed by the presence of the same phenotypical microorganism in at least two different samples. Interpretation of a single positive culture must be cautious and taken together with other evidence. A single positive result due to a low virulence organism or common contaminant does not confirm the presence of infection, and is generally considered a contaminant. Conversely, for high-virulent organism, uncommon contaminants or antimicrobial exposure, one positive sample is highly suggestive for infection (5, 19). The prevalence of culture-negative infections has been reported up to 34% of cases (average 5%-12%), but most of them appears to be caused by prior antimicrobial exposure (5, 11). Inability to identify a pathogen can also be caused by inadequate number of samples, long transportation time, slow growing microorganisms, and infections due to mycobacteria, fungi and fastidious bacteria. In culture-negative PJI, antimicrobial washout period of 2 weeks and a repeated aspiration at the end may be considered. Moreover, a greater number of samples should be collected, and the incubation period should be prolonged using molecular methods or techniques of biofilm-dislodgement. These techniques include sonication and ditiotreitolo. Sonication of the implants increases sensitivity and specificity of cultured organisms in chronic infections when compared with periprosthetic tissue culture (8).

6.6. Imaging studies

Plain radiographs. In suspected PJI, conventional radiograph has to be performed first, as it can evaluate bony structure around the implant (2, 53). The sensitivity and specificity of X-ray in the diagnosis of infection are very low (14% and 28-70%, respectively) (2, 54). Plain radiographs may document suggestive signs, as prosthetic loosening, radiolucency or osteolysis, periostal reaction (55). However, these are late and non-specific findings, and may be observed in both infected and aseptic failure (54, 55). Radiographs have the greatest utility when serial studies are performed over time. A new and rapid development of a continuous radiolucent line of greater than 2 mm or focal osteolysis within the first 3 years after surgery are indicative of infection (54).

Ultrasonography (US). US has a controversial role, as it presents a low sensitivity and specificity in detecting PJI (2, 53). US is useful in identifying fluid collections and joint effusions around the prothesis, and can be used to guide joint aspiration and biopsy (54, 55-57). Anterior distension of the capsule seems not predictive of infection (57).

Computed Tomography (CT). CT allows evaluation of signs of infection in the periprosthetic tissues, including periarticular fluid collections, joint effusion, and sinus tract (2, 58). As reported by Cyteval et al., the detection of capsular distension upon CT imaging was highly sensitive (83%) and specific (96%), with accuracy of 94% in diagnosing PJI (59). Moreover, they found that the presence of periprosthetic tissue alteration has an accuracy of 89%, with a sensitivity and specificity rate of 100% and 87%, respectively. Soft tissue collections and periosteal reaction showed poor sensitivity (41% and 16%, respectively), but high specificity (59). CT is also helpful to guide aspiration procedure.

Magnetic Resonance Imaging (MRI). MRI displays greater resolution for periprosthetic soft tissue abnormalities than CT. Using adjustment in the image acquisition parameters, MRI has sensitivity between 78% and 95% and a specificity ranging from 86% to 97% (2, 53, 60). MRI shows a high accuracy for PJI in detecting periosteal reaction, capsular and intramuscular edema. Galley et al. found that the difference between the PJI and control groups was significant for periosteal reaction, capsular edema, subcutaneous and intramuscular edema, and subcutaneous fluid collection in the area of surgical approach (60). They concluded that the presence of periosteal reaction, capsular and intramuscular edema were most significant for diagnosing PJI, with a mean sensitivity and specificity of 78% and 90%, 83% and 95%, 95% and 86%, and an accuracy rate of 86%, 91% and 89%, respectively (60).

Bone scintigraphy. Three-phase bone scintigraphy is one of the most widely used imaging techniques in

the diagnosis of PJI. The tracer is accumulated in areas of high metabolic activity, and the intensity of uptake is measured at three different time points, corresponding to blood flow (immediate), blood pool (at 15 minutes), and late (at 2 to 4 hours). Uptake at the prosthesis interfaces at the blood pool and late time points suggests PJI (5). Bone scintigraphy has an excellent sensitivity (68-88%), but its specificity is low, ranging from 18% to 71% (53, 54). As positive uptake in delayed-phase imaging due to increased bone remodelling around the prosthesis is normally present in the first 2 years after surgery, aseptic loosening cannot be differentiated from infection (53, 54). Therefore, three phase bone scintigraphy is only reliable two years after hip arthroplasty. Uptake of bone-seeking radiopharmaceutical is also well known in areas of sterile inflammation, such as osteolysis induced by polyethylene wear debris and heterotopic ossification (54). Due to its lack of specificity and high negative predictive value, bone scintigraphy is generally used as initial screening method to rule-out infection in patients with a low pre-test probability (53, 57, 61). A positive three-phase bone scintigraphy should suggest to perform labelled leukocytes scintigraphy, as this association increases the diagnostic accuracy, with a reported sensitivity and specificity of 80% and 99.5%, respectively (61).

WBC scintigraphy . WBC scintigraphy is regarded as the gold-standard technique for diagnosing neutrophil-mediated process (53). Images should be acquired at three different time points: early (after 30-60 minutes from radiopharmaceutical injection), delayed (after 2-4 hours), and late (after 20-24 hours). A different distribution and kinetics exist in inflammatory and infectious cases: infection exhibits an increased uptake in extension and/or size in late images, whereas inflammatory pattern shows a decreased or stable over time uptake (53). This imaging study has high values of sensitivity and specificity, with a negative-predict value of 92-100% and a diagnostic accuracy rate of 83-98% (2, 54). Due to its high negative predictive value, a negative WBC scan is sufficient to exclude a PJI (53). However, some studies reported both low sensitivity and specificity of this technique (61). These results have been attributed to the presence of chronic or low-grade infection and the possible influence of administered antibiotics. Concomitant antimicrobial therapy is thought to reduce diagnostic accuracy, but this is still controversial (62). Limitations of this technique are high cost, long-lasting, and biological risk in manipulation of potentially infected blood products. WBC scintigraphy in combination with bone marrow imaging or single photon emission computed tomography (SPECT/CT) is recommended to improve the accuracy to values of 83-98%, and it is useful for evaluating localization and extension of the infection (2, 53).

18-Fluorodeoxyglucose positron emission tomography (FDG-PET-CT). PET-CT is a fast imaging for detection of PJI, with reported sensitivity of 82-86% and specificity of 86-87%, and a high negative predictive value (58). However, false positive results may occur in aseptic loosening and in the early postoperative period for the physiological uptake up to 3 postoperative months (58). Different interpretation criteria have been proposed, and inconsistent results of diagnostic accuracy have been reported. Data concerning the sensitivity and specificity show high variability, ranging from 33% to 95% and 39% to 96%, respectively (53). A qualitative interpretation is thought to be more reliable than a quantitative one. Verberne et al. stated that the most accurate finding of PJI was FDG uptake extending along the femoral bone-prosthesis-interface at the middle portion of the stem, with a sensitivity of 81% and specificity of 94% (63). A physiological, non-specific uptake around the head and neck is commonly seen in 80% of cases, due to component's wear. Moreover, physiologic uptake may occur at the lateral and medial sides of the acetabular cup, at the proximal part, and at the distal tip of the femoral stem (63). Few studies compared PET-CT directly to WBC scintigraphy, showing that PET-CT has higher sensitivity but lower specificity in detecting PJI, with an overall diagnostic accuracy of 65-90% for PET-TC and 70-95% for WBC scan (64). Sconfienza et al. stated that WBC scan should be performed within 2 years after prosthesis implantation, whereas 3-phases bone scan or FDG-PET should be done more than 2 postoperative years if infection is suspected (2). Romanò et al. concluded that bone scan and FDG-PET should be performed in patients with low pre-test probability of infection (53). WBC scintigraphy should be reserved in cases of high suspicion of infection or to differentiate between aseptic/septic loosening: a positive WBC scan is considered a confirmative criteria (2, 53, 63).

6.7. Molecular diagnosis

Infections caused by low virulent organisms, lack of viability during transport, or prior antimicrobial use could be associated with culture-negative infections. Molecular methods, such as PCR, next generation sequencing (NGS), and metagenomic shotgun sequencing could overcome these limitations (65). However, disadvantages include detecting DNA from dead bacteria, contaminating environmental bacteria or human tissue, and the inability to identify all organisms in polymicrobial infections (8, 65).

7. Conclusion

Diagnosis of PJI is still challenging for the lack of a gold-standard definition as well as of a single diagnostic test with an accuracy of 100%. To date, diagnosis is based on a multidisciplinary and combined approach which assesses clinical findings, serum and synovial biomarkers, radiological investigations, histological evaluation, and microbiological analysis. However, diagnostic accuracy is weakened by previous antimicrobial exposure, potential for contamination, and lack of specificity of inflammatory parameters. New testing modalities, including molecular methods, and novel synovial fluid markers are promising as additional tools in the diagnosis of PJI. However, further studies are required to define optimal threshold value of serum and synovial biomarkers, and to increase the diagnostic accuracy of current investigation techniques.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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