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REVIEW ARTICLE

Evaluation and interpretation of prosthetic joint infection diagnostic investigations

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Abstract

Background Total joint arthroplasty (TJA) is considered one of the most successful surgical procedures ever developed. It can successfully provide pain relief, restore joint function, and improve mobility and quality of life. Prosthetic joint infection (PJI) presents with a wide variety and severity of signs and symptoms. It remains a major threat to the outcome of TJA procedures and usually necessitates surgical intervention and prolonged courses of antibiotics. Inappropriate treatment of an unrecognized PJI usually ends with unacceptable and sometimes catastrophic results.

The aim The understanding and evaluation of diagnostic investigations are extremely important to properly diagnose PJI, including frequently unrecognized low-grade infections, and to provide healthcare professionals with needed information for the care of patients affected by this condition. This article aims to review most of the methods available in PJI diagnostics, to emphasize the strengths and the weaknesses of each of them, and to provide a guideline on how to select the surgical treatment strategy based on the level of diagnostic certainty during the evaluation period. To safely accomplish this, it is crucial to be aware of the limitations of each diagnostic modality.

The focus The emphasis will be on the use and interpretation of the core criteria for PJI diagnosis, including the pathognomonic sinus tract communicating with the implant, purulent synovial fluid, inflammation in the periprosthetic tissue, cell count with differential, microbial growth in the synovial fluid culture, tissue sample cultures, and sonication samples.

Keywords Prosthetic joint infection · Prosthetic joint replacement · Diagnostic criteria · The algorithm

Introduction

TJA (total joint arthroplasty) failures include a wide variety of clinical presentations [1, 2]. PJI (prosthetic joint infection) represents the second most frequent, but also the most important complication of TJA after aseptic loosening. The number of PJI is increasing because of the larger number of arthroplasty surgery worldwide and the growing awareness of "low grade" PJI [3]. PJI may present as an acute fulminant disease with sepsis but it could be also completely asymptomatic [4]. Most of the PJIs present with signs and symptoms between these two extremes. High-grade PJI can be a life- or limb-threatening condition necessitating immediate action. However, it is usually easy to diagnose. Whereas low-grade PJI is mostly presenting with early loosening, or pain only, it can be very difficult to diagnose. During recent years, we have become increasingly aware that, in addition to obvious PJI, there is an important but unknown number of septic failures—PJI hiding within "aseptic failure" cohorts [5–7]. Recent papers are presenting significant numbers of up to 20% of low-grade PJI within presumed aseptic failure cohorts [7, 8]. Many early failures after revision TJA fit within this overlooked PJI group [7–10]. The main challenge of the diagnostic evaluation is to accurately differentiate between septic and aseptic TJA failure because the treatment is different (Table 1).

There is still no single test to reliably diagnose all PJIs. Therefore, a variety of different combinations of diagnostic tests were proposed to improve the accuracy of the PJI diagnostics. There are currently five popular diagnostic criteria available for PJI: Musculoskeletal Infection Society (MSIS), Infectious Disease Society of America (IDSA), International Consensus Meeting (ICM), ProImplant, and European Bone and Joint Infection (EBJIS). The main differences among them are the selection and rank of the included diagnostic investigations

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Table 1 Differences in treatment between aseptic total joint failures and PJI

Differences in treatment between aseptic total joint failures and PJI:
• One-stage replacement is the treatment of choice for aseptic TJA failure, while for PJI the surgical options include three types of procedures: debridement surgery with implant retention (DAIR), one-stage exchange (OSE), and two-stage exchange (TSE)
• With aseptic failure, synovectomy–debridement is limited to the amount needed for proper implant exchange, while a more aggressive debridement is needed in all PJI and nearly complete debridement in DAIR and OSE
• Extended antibiotic treatment is necessary for the treatment of PJI but not for the treatment of aseptic TJA
• Partial revisions are normal in aseptic failures but only exceptionally indicated in PJI

resulting in sensitivity and specificity differences. The use of specific but not sensitive criteria raises the possibility of missing a significant proportion of PJI, while the use of sensitive but not specific criteria means that some of the patients with aseptic failure would be diagnosed as septic. The consequence of the suboptimal accuracy of the diagnostic criteria available is that misdiagnosed patients are not treated appropriately. Patients with misdiagnosed PJI receive inadequate treatment in terms of surgical and antimicrobial aspects [7, 9]. If low-grade PJI is not recognized and treated properly, infection generally persists, and it can lead to early loosening and multiple revisions with functional loss and disability severely impairing the quality of life [9, 11–13]. In contrast, by increasing PJI diagnostic sensitivity, aseptic conditions may be diagnosed as septic with the consequent over treatment. The incidence and morbidity of under diagnosed PJI are significant and relatively well documented, while the incidence and negative consequences of overtreatment of aseptic failures as PJI have not yet been thoroughly analyzed. By selecting sensitive criteria for less invasive treatment options and specific criteria for more aggressiveness, we can minimize the damage incurred due to the suboptimal PJI diagnostic accuracy of the available diagnostic criteria and diagnostic tests.

The treatment of PJI is complex including surgery and prolonged antibiotic therapy [14, 15]. After surgery, antibiotics are given intravenously for one to three weeks continuing orally for additional ten weeks. If the implant is retained or directly exchanged antibiofilm antibiotics, rifampicin for staphylococci and quinolones for Gram-negative agents improve significantly the chances for a cure. Surgical treatment of PJI includes three main options:

1. Debridement and implant retention (DAIR), indicated in early acute PJI if radicaldebridement is feasible when the biofilm is still immature, mostly up to four weeks after implantation, or in late acute presentation after haematogenous spread
2. One-stage exchange (OSE) is mostly indicated in chronic PJI if radical debridement is feasible
3. Two-stage exchange (TSE), indicated for most remaining PJI presentations

Other treatment possibilities, antibiotic suppression, iatrogenic sinus tract formation, and amputation are reserved for special circumstances. The selection of the best surgical option depends on the presumed duration of infection, debridability, microbiology, and to a lesser extent the degree of bone and soft tissue loss, implant type, and general patient conditions. An artificial joint is considered debridable, when it is possible to remove a sizable layer of the infected, necrotic, and granulomatous or fibrotic tissues all around the artificial joint cavity without removing functional tissues such as nerves, major vessels, and tendons [14].

The main guideline for the selection of the best care for PJI patients is to select the least invasive treatment option for the best functional result and without compromising the microbiological cure.

In comparison to the reviews available to date, the presenting review emphasizes the strengths, the weaknesses, and the evidence of each of the diagnostic modality and places the whole diagnostic process into clinical context, providing guidelines for surgical treatment.

Patient evaluation

The evaluation of the patient with a presumed PJI aims to obtain all the necessary information for optimal treatment planning. The process includes PJI diagnostic procedures for accurate detection of all types of PJI and/or exclusion of many differential diagnoses that can clinically mimic PJI but also the assessment of the general medical condition and the status of the affected joint. The diagnostic process starts before surgery and ends after all intraoperative examinations are completed. Until then, the patient should be treated as having a PJI. Close cooperation among various specialists including orthopaedic surgeons, infectious disease experts, microbiologists, and pathologists is needed [16].

General clinical evaluation is required for assessing the severity of the PJI, the comorbidities that may influence the treatment plan, and to identify the eventual visceral or musculoskeletal origin of TJA pain that can mimic PJI. Pain in the artificial joint may result from other conditions, and therefore assessment of the spine and other ipsilateral joints is also necessary [11, 13, 17, 18].

Patients with clinical signs of acute PJI showing systemic symptoms such as fever and local pain, erythema, oedema, and impaired prosthetic joint function should have a preoperative diagnostic aspiration and be prepared for surgery as soon as possible. The pre-operative evaluation is crucial because even in patients with clear clinical presentations of the acute PJI clinical picture can be also due to aseptic reasons, or the septic process is not involving the joint [11, 13].

Less acute patients presenting with clinical symptoms of PJI should undergo an evaluation with a thorough workout to

determine the probability of PJI. This helps in the decision about the treatment plan. Pre-operative investigations for PJI are limited to the aspiration for cytology and microbiology and bone scans. Since these are frequently inconclusive, the probability of PJI based on patient history is crucial for the decision between the septic or aseptic treatment pathway. Clinical symptoms and signs indicating a high degree of probability for PJI are presented in Table 2 [11].

The laboratory evaluation should be tailored to support the general assessment of the patient before the eventual surgical procedure. C-reactive protein (CRP) is generally elevated in PJI but is often normal in low-grade PJI. Along with the history and clinical evaluation, it can be helpful in the selection of patients suitable for the PJI diagnostic process.

A recent plain radiograph of the affected joint should be obtained, and, if clinically indicated, of other joints and the spine. Other imaging modalities may be needed for surgery planning and for ruling out aseptic conditions potentially affecting the failed prosthetic joint.

It is essential to perform a systematic general and joint-specific evaluation to determine the probability of PJI in all unclear situations with the joint pending revision.

Diagnostic investigations for PJI evaluation

Different diagnostic criteria reflect the wide range of tests available for PJI diagnostics. In general, it is important to consider at least clinical, histological, cytological, and microbiological parameters when selecting PJI diagnostics.

Clinical diagnosis

There are two clinical pathognomonic features of PJI: sinus tract communication with the implant and purulence around the implant. There is a universal agreement that a sinus tract communicating with the joint confirms PJI. When there is doubt if the sinus is extending into the joint cavity, the injection of methylene blue into the joint is the best way to obtain the diagnosis. If the methylene blue leaks out from the sinus, the diagnosis is confirmed. Purulence needs to be interpreted with greater caution because a range of conditions can cause macroscopically purulent but aseptic synovial liquid. The most frequent reasons are adverse tissue reactions associated with metal-on-metal attrition in the TJA (due to metal-on-metal bearing or any other situation where there is dynamic contact between metallic materials and other metallic or ceramic components) and/or corrosion [19]. Aseptic purulence can also result from crystal, reactive, or inflammatory arthritis [20, 21]. After excluding these possibilities, purulence is no longer a controversial criterion and has close to 100% specificity.

Table 2 Clinical presentation indicating a high probability for PJI [11]

Clinical presentations indicating high probability for PJI:
• Early or late acute onset of inflammation signs (i.e., pain, swelling, warmth, or redness around the prosthetic joint region)
• Persistent wound drainage
• Painful prosthetic joint with no other reason for pain, particularly with no pain-free interval after original implantation
• Early loosening or osteolysis, particularly in well-positioned TJA
• Repeat dislocations
• Prolonged antibiotic administration after primary TJA
• Recent bacteremia (pedicure, dental procedures, infections, etc.)

Histological diagnosis

Histology is a standard, well-studied diagnostic modality with evidence indicating sensitivity and specificity above 90%. The diagnosis depends on the concentration of neutrophils in the periprosthetic membrane or capsular tissue (the former providing more accurate analysis). A comprehensive review of the available evidence regarding how to harvest, perform, and utilize the histological techniques has been published recently [22]. The presence of PJI is usually determined by the count of neutrophils per high-power field at 400-times magnification [23]. Different researchers have offered ranges from ≥ one to ≥ ten neutrophils per high-power field [24]. Neutrophils can also be detected with immunohistochemical techniques and validated by histopathological scores [25]. By using the CD15 focus score, the optimum threshold for diagnosing PJI was defined as 39 CD15+ neutrophil granulocytes/focal point. Histopathology differentiates to some extent between high or low virulence PJI [26, 27].

Recently a standardization of histopathological findings with a new classification based on clear morphological criteria that cover the complete spectrum of histopathology in the periprosthetic membrane has been proposed. The classification has the following seven distinct pathological types: I, particle-induced; II, infection; III, combination; IV, indifferent; V, arthrofibrotic; VI, allergic/immunological/toxic adverse reactions; and VII, bone pathologies [26].

Cytological diagnosis

Joint aspiration is the single most important pre-operative diagnostic tool used for evaluating patients for suspected PJI. It should be performed in every painful prosthetic joint before surgical revision. To avoid dry tap, it is advisable to use advanced imaging including CT or ultrasound for needle guidance to the synovial fluid pouch [28–30]. Joint aspiration is the only pre-operative test that can discover the causative microbiological agent. It is perhaps even more important for leukocyte count and differential determination and represents

the simplest, most rapid, and accurate test for differentiating between PJI and aseptic failure. Several cutoffs have been proposed by different authors [24, 25, 31–35]. If DAIR and OSE are planned, sensitive PJI diagnostic cutoffs should be considered. Recent studies using sensitive methods such as sonication suggest 2000 leukocytes/μL and 70% granulocytes as the optimal composite cutoff value [24, 31, 32]. Since the cell count (as well as histology) depends on the inflammatory induction capacity (virulence) of the causative organism, it is expected that a lower threshold would be needed for shoulder PJI because of the higher proportion of low virulence organisms (e.g., *Cutibacterium* species). For optimal interpretation of the cell count, it is necessary to take into consideration the special circumstances outlined in Table 3.

Microbiological diagnosis

Microbiological diagnosis is based on the culture of the synovial fluid taken either before or during surgery, cultivation of intra-operative tissue samples, or cultures of the sonication fluid. There is limited evidence on exploratory tissue sampling in PJI diagnostics. It could be considered a last resort if a comprehensive pre-operative evaluation of a painful TJA does not result in a diagnosis. Swabs have no place in PJI diagnostics [37].

Synovial fluid culture

Synovial fluid culture is not very sensitive. A recent meta-analysis showed a pooled sensitivity of 72% and a specificity of 95%. Other studies showed the sensitivity between 45 and 75% with a specificity of 95% [38–40]. Inoculation of the synovial fluid in blood culture media improves sensitivity and decreases problems with long transport, delayed processing, and inadequate transport media. The pediatric blood culture bottle requires a low volume of synovial fluid which makes it the ideal choice when a limited amount of synovial fluid is available [41]. A long incubation time of 14 days or more is necessary to detect low virulent and difficult-to-detect pathogens such as the *Cutibacterium* species. One positive synovial fluid culture is insufficient to diagnose PJI. If also the second culture is positive for the same organism, the specificity is high enough to confirm the diagnosis. A combination of one positive synovial fluid culture and a positive cell count or differential is also diagnostic.

Table 3 Special circumstances for the interpretation of cell count [36]

Cell count has to be interpreted carefully under the following conditions:
• Leukocyte cutoff values are not interpretable within 6 weeks after implantation
• False-positive values can be for rheumatic joint disease, crystal periprosthetic arthritis, and reactive arthritis
• False-negative can be in the presence of sinus tract
• Leukocyte count can be determined as early as 20 min into surgery as a point-of-care investigation

Tissue samples

Tissue sample cultivation is the most important intra-operative diagnostic procedure. From five to six intra-operative tissue samples have been calculated as the optimal number for microbiological investigations. The sensitivity of tissue cultures ranges from 65 to 94% [42]. Intra-operative swabs are not useful for PJI diagnostics due to their low sensitivity [43]. Superficial wounds or sinus tract swabs can be particularly misleading and should be avoided because the frequency of detecting colonizing rather than infecting organisms is too high.

Sonication

Sonication was introduced by Tunney in the 1990s and then popularized by Trampuž [44]. It is based on low-frequency ultrasound waves passing through the liquid surrounding the prosthesis for the detachment of biofilm microorganisms from the implant surfaces. To avoid contamination, explants should be directly placed in a sterile, airtight container in the operating theatre and not in a plastic bag [45]. The sonication fluid is inoculated on aerobic and anaerobic plates and cultured. Inoculation of the sonication fluid in blood culture bottles probably improves the sensitivity and reduces the cultivation time [46, 47]. A cutoff value of 50 colony-forming units (CFU)/ml of sonication fluid yields a sensitivity of 79% and a specificity of 99% for the diagnosis of PJI [44]. In most studies, the culture of sonication fluid shows superior sensitivity compared with the culture of multiple periprosthetic tissue samples [44, 48]. In one study, sonication had similar sensitivity as tissue biopsies, but the combination of the two had the highest sensitivity [49]. Sonication is particularly appropriate for patients who are receiving or have recently received antibiotic treatment and in chronic PJI with mature biofilm. Sonication of implants with a covering of antibiotic-loaded bone cement or bone cement itself may inhibit bacterial growth and lead to false-negative results caused by increased antibiotic elution during sonication [50]. It is thus preferable to take implant parts for sonication before removal of bone cement because high amounts of antibiotics are released from antibiotic-loaded bone cement during cement cracking.

Gram staining

Gram staining for detecting living organisms in the synovial fluid has very low sensitivity accompanied by 100%

specificity. The examination is usually positive in high-grade PJI, which is generally easy to diagnose. Gram staining can be particularly effective in ambiguous cases associated with crystal or inflammatory arthritis or with an infection. If positive, it gives immediate confirmation of the diagnosis and is very helpful for the selection of empirical antibiotics by distinguishing between Gram-positive and Gram-negative organisms [41].

The significance of other traditional and novel tests for PJI diagnostics

Several other tests in the diagnostic armamentarium can be useful for evaluating patients with suspected PJI. However, each of them has certain strengths and shortcomings.

Serologic tests

Routine blood tests like white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT) are useful for the general evaluation of patients but do not have sufficient sensitivity or specificity to diagnose or exclude PJI [42, 51]. Patients with low-grade PJI frequently have normal systemic inflammatory markers [52]. CRP is normal in around 30% of culture-proven PJI [51]. CRP is elevated after surgery, reflecting post-interventional inflammation, and gradually decreases afterward [53]. Itself, it has a limited role in the evaluation of PJI, but it is important for the early postoperative follow-up of patients after PJI treatment [54]. Erythrocyte sedimentation rate (ESR) is becoming obsolete because it is not sufficiently specific [55]. Novel serum markers based on coagulation-related indicators, such as D-dimer and serum fibrinogen that detect fibrinolytic activity, have been proposed for pre-operative detection of PJI. The results of initial studies are controversial with specificity and sensitivity within the same range as CRP [56].

Alpha defensin

Defensins are antimicrobials secreted by neutrophils when microorganisms target during infection [57]. Alpha defensin (AD) has been extensively studied as a biomarker for the detection of PJI [57, 58]. There are two AD tests: the fast lateral-flow qualitative test (ADFL) and the quantitative ELISA test. Gehrke et al. demonstrated similar accuracy of both tests on a high number of patients with the same criteria with no significant difference in sensitivity and specificity in the synovial fluid between the two test types [59]. ADFL is a qualitative test for detecting AD in synovial fluid and can be performed during surgery in the operating theater or within ten minutes of any joint aspiration. The first studies, mostly based on MSIS criteria, have shown AD as a promising marker [60]. In recent studies, with more sensitive definition criteria,

Table 4 PJI is diagnosed if at least one of the following clinical, histological, cytological, or microbiological criteria is met within the limitations defined below

Diagnosis of PJI:
Clinical
1. Sinus tract communicating with the implant
2. Purulent synovial fluid[a]
Histological
1. Inflammation in periprosthetic tissue[b]
Cytological
1. > 2.000 leukocytes/μl or > 70% neutrophils/μl[c]
Microbiological
1. Synovial fluid culture[d]
2. Tissue samples culture[e]
3. Sonication[f]

[a] Not applicable in crystallopathies, inflammatory joint disease, metallosis, reactive arthritides

[b] Different criteria available

[c] Consider also joint-specific values in references from the appropriate paragraph

[d] Together with tissue samples (or two samples from two aspirations) growing the same organism with the same susceptibility pattern

[e] Identification of the microbe in the endoprosthetic tissue samples or/and in the synovial fluid sample ≥ two tissue samples out of three or more collected growing the same organism with the same susceptibility pattern

[f] In general ≥ 50 CFU/ml or ≥ one CFU/ml for highly virulent pathogens or patients receiving antimicrobial treatment

ADLF showed much lower sensitivity (54.4−77%) while the specificity remained high at 99.3% [13, 61]. The test is not suitable for screening because of its low sensitivity but it remains a good confirmatory test because of its high specificity. Compared to a more sensitive cell count, ADFL is associated with higher costs and lower availability.

Leukocyte esterase

Leukocyte esterase has been proposed as an off-label application for intra-operative diagnostics of PJI. A high percentage—up to 33% of non-readable tests—is the main disadvantage of the method [59]. Another shortcoming is a difficult interpretation of the intermediate results. Nevertheless, it has the advantage of being a cheap and fast test suited for the intra-operative application.

Emerging diagnostic modalities

Insufficient specificity is a common problem with DNA-based molecular diagnostics but the perspective is promising and its role is growing [62–64]. Its main importance is in culture-negative infections, providing a clue to the potential etiologic agent. There are other emerging tests including synovial CRP, synovial cytokines, calprotectin, and adenosine deaminase

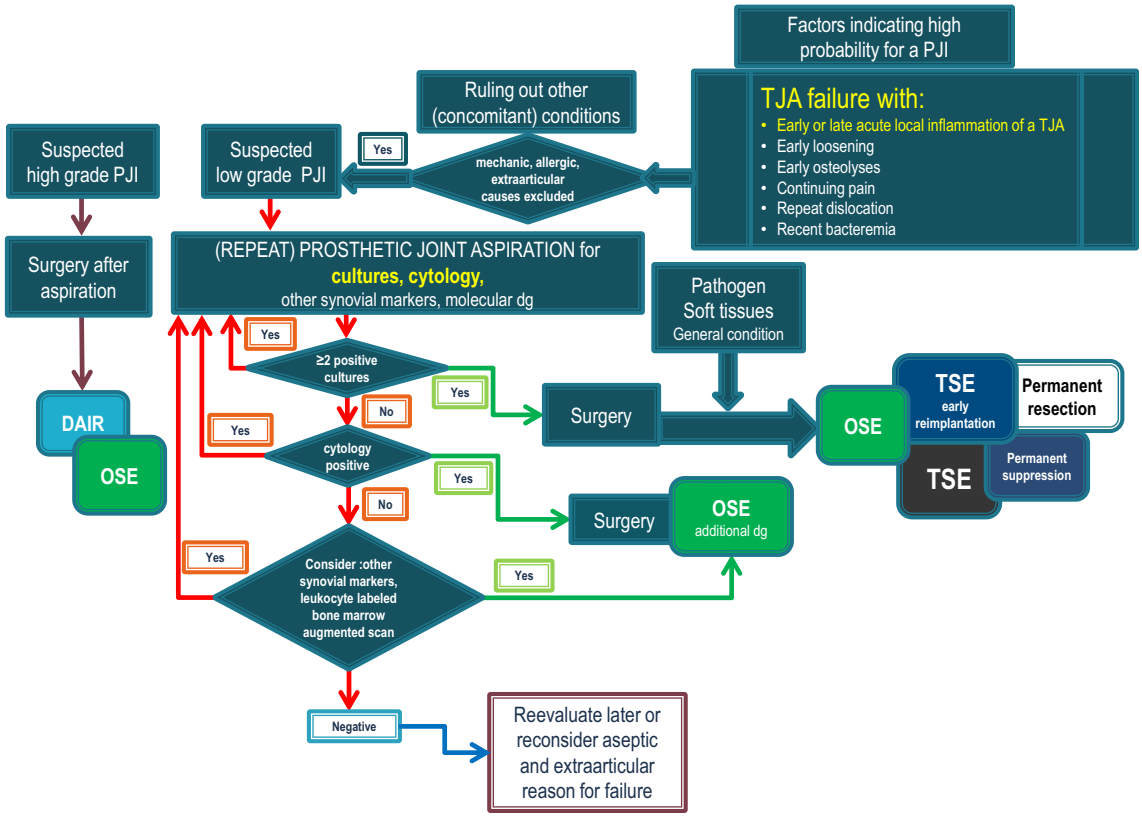

Fig. 1 Diagnostic algorithm and treatment options for different PJI scenarios. TJA, total joint arthroplasty; DAIR, debridement, antibiotics, and implant retention; OSE, one-stage exchange; TSE, two-stage exchange

that also show diagnostic promise. Most of these tests have not been extensively studied and some are not readily available [34, 65, 66]. D-lactate is a new synovial marker with high PJI diagnostic potential because it is secreted by the bacteria rather than by the host defense cells [67].

The role of nuclear imaging in diagnosing PJI is evolving. This modality is important because it helps determine the pre-operative probability of PJI. The three-phase bone scintigraphy is not useful in the first 2 years due to bone remodeling around the prosthesis. But after two years, it detects a pathologic process around the joint. Although it is not very specific for PJI, it has a high accuracy for ruling out PJI. The labeled leukocyte scan is probably the best nuclear imaging modality available for PJI diagnostics, particularly if augmented with a bone marrow scan to avoid a false-positive outcome in patients with active bone marrow around the failed TJA. The sensitivity and specificity are high in active PJI but not yet determined for low-grade PJI [68].

Conclusions

In aseptically failed TJA, the expected treatment outcomes and the probability of the complications need to be compared to the disabilities incurred by the failed joint. Frequently the potential harms of the treatment and expected outcome do not justify intervention. In PJI, the situation is different in the case of high-grade processes where treatment is saving life or limb. However, it is similar in many low-grade PJI, where the quality of life even after successful extensive treatment of the PJI may be lower than the quality of life before treatment due to treatment-incurred systemic or local damage and/or complications.

The diagnostic threshold for PJI should be considered along with the planned surgical modality. DAIR and OSE require sensitive diagnostic criteria, while invasive TSE requires specific criteria. Although it is preferable to diagnose PJI before surgery, it is frequently not possible. When the probability for PJI is low, repeat aspirations for cell count determination and microbiology, as well as bone scans, can be helpful in pre-operative diagnostics. In patients with probable but pre-operatively not confirmed PJI, DAIR, or a complete OSE with a radical debridement, is the treatment of choice depending on the timing of presentation. The definite confirmation (or rejection) of the diagnosis of PJI occurs during the early post-operative period. Consequently, empiric antibiotic therapy should be initiated post-operatively until the results of cultures and histology are available.

Practical diagnostic criteria for PJI consist of clinical, histological, cytological, and microbiological tests. The criteria presented in Table 4 are easy to remember and apply, though the limitations in the footnotes must be considered as the specific clinical situation remains the most important element for diagnostic and treatment decisions. Figure 1 provides the diagnostic algorithm together with treatment options for different PJI scenarios.

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