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Diagnosis of peripheral bone and prosthetic joint infections: overview on the consensus documents by the EANM, EBJIS, and ESR (with ESCMID endorsement)

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Abstract

Objectives Peripheral bone infection (PBI) and prosthetic joint infection (PJI) are two different infectious conditions of the musculoskeletal system. They have in common to be quite challenging to be diagnosed and no clear diagnostic flowchart has been established. Thus, a conjoined initiative on these two topics has been initiated by the European Society of Radiology (ESR), the European Association of Nuclear Medicine (EANM), the European Bone and Joint Infection Society (EBJIS), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The purpose of this work is to provide an overview on the two consensus documents on PBI and PJI that originated by the conjoined work of the ESR, EANM, and EBJIS (with ESCMID endorsement).

Methods and results After literature search, a list of 18 statements for PBI and 25 statements for PJI were drafted in consensus on the most debated diagnostic challenges on these two topics, with emphasis on imaging.

Conclusions Overall, white blood cell scintigraphy and magnetic resonance imaging have individually demonstrated the highest diagnostic performance over other imaging modalities for the diagnosis of PBI and PJI. However, the choice of which advanced diagnostic modality to use first depends on several factors, such as the benefit for the patient, local experience of imaging

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specialists, costs, and availability. Since robust, comparative studies among most tests do not exist, the proposed flowcharts are based not only on existing literature but also on the opinion of multiple experts involved on these topics.

Key Points

- *For peripheral bone infection and prosthetic joint infection, white blood cell and magnetic resonance imaging have individually demonstrated the highest diagnostic performance over other imaging modalities.*
- *Two evidence- and expert-based diagnostic flowcharts involving variable combination of laboratory tests, biopsy methods, and radiological and nuclear medicine imaging modalities are proposed by a multi-society expert panel.*
- *Clinical application of these flowcharts depends on several factors, such as the benefit for the patient, local experience, costs, and availability.*

Keywords Osteomyelitis · Prosthesis-related infections · Clinical laboratory techniques · Radiology · Nuclear medicine

Abbreviations

AGA	Anti-granulocyte antibody
CRP	C-reactive protein
CT	Computed tomography
EANM	European Society of Nuclear Medicine
EBJIS	European Bone and Joint Infection Society
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESR	Erythrocyte sedimentation rate
ESR	European Society of Radiology
FDG-PET	Fluorodeoxyglucose-positron-emission tomography
HMPAO	Hexamethylpropylene amine oxime
MRI	Magnetic resonance imaging
OCEBM	Oxford Center for Evidence-based Medicine
PBI	Peripheral bone infection
PICO	Population/problem, intervention/indicator, comparator, outcome
PJI	Prosthesis joint infection
SPECT	Single-photon emitting computed tomography
WBC	White blood cell

Introduction

Peripheral bone infection (PBI) and prosthetic joint infection (PJI) represent two different infectious conditions of the musculoskeletal system [1, 2].

PBI include osteitis and osteomyelitis. Osteitis is a periosteal bacterial infection, which can develop acutely (< 8 weeks) or chronically (> 8 weeks) after trauma or surgery [3]. Osteomyelitis is classified into acute or chronic, too. Acutely, necrotic bone and bacteria are detected concurrently. Progression to chronic osteomyelitis is characterized by the presence of avascular bony fragments (*sequestra*) [4]. A strong periosteal reaction usually develops around the infection, with or without the presence of a sinus tract. PBI incidence is low, accounting for about 2% per year in developed countries, with slightly increase after surgery (2–4%), or trauma surgery with potentially contaminated fracture (19%), or in immunocompromised hosts [5–8].

PJI is a complication of joint replacements [9]. Its incidence ranges from 2 to 2.4% for newly implanted prostheses, while it may reach up to 20% for revision procedures. Due to general population aging, the number of replaced joints is increasing. Thus, PJI represents a non-negligible health issue, leading to repeated surgery, prolonged hospitalization, increased morbidity, and increased costs [10, 11]. PJI can be differentiated as early (within 3 months from surgery), delayed (between 3 months and 2 years), and late (over 2 years). At any stage, PJI may present with a quite insidious onset and non-specific symptoms; thus, its diagnosis may be challenging [12–15].

No single routine test alone can diagnose PBI and PJI with sufficient accuracy. In most cases, imaging, clinical, microbiological, and laboratory examinations are performed based on their availability, physicians' experience, and economic considerations. Regarding PBI, current recommendations for its diagnosis are scarce, mainly based on local experiences, or lacking a multidisciplinary approach [5]. Regarding PJI, literature is richer; however, many recommendations still lack multidisciplinary approach, are not updated on the most recent imaging modalities, or fail providing a possible diagnostic flowchart [5].

Thus, an expert panel of radiologists, nuclear medicine physicians, orthopedic surgeons, and infectious disease specialists representing the European Society of Radiology (ESR), the European Association of Nuclear Medicine (EANM), the European Bone and Joint Infection Society (EBJIS), and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), respectively, performed a thorough systematic literature review and developed two consensus documents on the diagnostic management of PBI and PJI, with emphasis on radiologic and nuclear medicine modalities. These documents were recently published in the *European Journal of Nuclear Medicine and Molecular Imaging* [16, 17].

Our purpose is to provide an overview on the two consensus documents on PBI and PJI produced by the ESR, EANM, and EBJIS (with ESCMID endorsement).

Working group, statements, literature search, and scoring system

Details on these aspects are presented in the original studies [16–19] and provided as Supplementary Material.

Diagnosis of PBI

Pain is the principal acute local symptom of PBI associated with reduced function [20]. Physical examination may show a fistula with pus discharge, although frequently only mild skin redness and swelling can be seen. When a skin breach is present, the probe-to-bone test can be performed, consisting in inserting a metallic probe in the breach trying to reach the bone. The concept behind this simple test is that if the probe can reach the bone, the same can be done by infectious bacteria [21]. In chronic cases, however, symptoms are generally absent.

Statements

Full list of statements regarding PBI and their evidence levels is reported in Table 1.

- Clinical and laboratory parameters (statements no. 1 to no. 4, no. 7, no. 8)

When PBI is suspected, additional diagnostic tests may help confirming the diagnosis. If a skin breach is present, the probe-to-bone test can be performed. This represents a routine practice in the diagnosis of diabetic foot infection, although no clear evidence is published for PBI. Similarly, there is no evidence that a fistula directing to the bone and concurrent purulent discharge represent the proof of an underlying bone infection.

Regarding blood tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count determination should always be performed. Increased ESR and CRP may be present and may suggest the presence of infection. WBC counts are more rarely increased. In patients with acute foot osteomyelitis, positive predictive value for infection of ESR in patients without diabetes was 78%, and in those with diabetes was 81%, with 58% and 31% negative predictive value, respectively [22]. A cutoff of 0.4 ng/ml of serum procalcitonin has been reported to be sensitive and specific in the diagnosis of acute osteomyelitis [23].

Blood cultures become positive mostly in hematogenous osteomyelitis. There is little evidence supporting the use of blood cultures in the diagnosis of PBI outside the spine [24].

To replace bone biopsy, the value of sinus tract and deep tissue cultures has been tested [25–29], finding it to be inadequate to identify the correct pathogen in osteomyelitis. One study showed different result, involving two sinus tract cultures with bone contact at different times, showing 94% diagnostic accuracy in cases with two concordant cultures with bone contact [30]. Authors however conclude that this approach should not replace biopsy when this can be easily obtained.

Suspending antibiotic therapy prior to microbiological culture is a reasonable and common practice. However, regarding PBI, literature is insufficient to support or discourage this practice [30–32]. Thus, a good clinical practice should recommend that antibiotic administration is suspended or postponed only if feasible and reasonable, being the optimal duration of this suspension still not established.

- Radiological imaging techniques (statements no. 5, no. 6, no. 9 to no. 12)

In PBI, conventional radiography is the first modality to perform. However, conventional radiography becomes positive only after 7–14 days from symptom occurrence and when at least 30–50% of bone mass is lost. Sensitivity and specificity of conventional radiography in PBI range between 43–75% and 75–83%, respectively [33, 34]. Computed tomography (CT) has high resolution in the evaluation of peripheral bone; thus, it can replace conventional radiographs in anatomically complex locations (e.g., shoulder, pelvis). CT is particularly useful to detect bone sequestra and subtle findings such as gas bubbles and tiny area of cortical involvement [35].

In patients with clinical and imaging suspicion of PBI, current clinical practice suggests a percutaneous bone biopsy may be performed to identify the causative microorganism. However, evidence is low and conflicting. Some studies reported high accuracy (85.5–94%) [26, 30, 31] in identifying a single causative microorganism after biopsy. However, another study had low rate of positive specimens obtained by imaging-guided biopsy [32]. Superiority of open surgical biopsy has also been confirmed [26, 27, 36], remaining however a very invasive method of diagnosis.

Non-contrast magnetic resonance imaging (MRI) is pivotal in PBI, having 88–98% sensitivity, 70–96% specificity, and 81–86% accuracy [37–39]. MRI evaluates the involvement of both bone and soft tissues, being also able differentiating infection from other mimickers, such as bone tumors. Intravenous Gadolinium administration does not increase diagnostic performance but may help to better define the presence and extent of soft tissue abscesses and also to avoid overstaging by differentiating infection from edema [40]. Although no specific study addressed the issue of metallic fixation devices in patients with PBI, orthopedic implants in general do not represent a contraindication to MR examinations, with susceptibility artifact mostly limited to the profile of the implant itself [41].

- Nuclear medicine imaging techniques (statements no. 13 to no. 18)

Table 1 Statements on the diagnosis of peripheral bone infection

Item	Statement	Level of evidence
1	Patients presenting with clinical and radiological signs of peripheral bone infection or a positive probe-to-bone test may require further diagnostic procedures	5
2	Fistula direct to the bone and purulent discharge are evidence of bone infection	5
3	C-reactive protein, erythrocyte sedimentation rate, and white blood cell counts should always be performed in patients suspected to have peripheral bone infection for diagnostic purposes	4
4	Blood cultures should be considered in patients with fever suspected to have peripheral bone infection for diagnosing the involved bacteria	4
5	Conventional radiography is the first imaging modality to be performed in patients suspected to have peripheral bone infection for diagnosis and follow-up	3
6	In case of clinical and radiological signs of peripheral bone infection, bone biopsy is the reference standard for confirming infection and identifying the causative microorganism	4
7	In case of clinical and radiological signs of peripheral bone infection, sinus tract cultures and/or superficial swab cultures should be discouraged in the diagnostic workup; bone biopsy is the gold standard	4
8	Antibiotic therapy should be discontinued before biopsy	5
9	CT should be used as an adjunct to conventional radiographs in complex anatomic areas and is useful to detect bone sequestra	4
10	Non-contrast MRI has high diagnostic performance in detecting peripheral bone infection	2
11	Intravenous administration of Gadolinium-based contrast agents does not increase the diagnostic performance of MRI in peripheral bone infection	2
12	The presence of a metallic implant/fixation device is not a contraindication to perform MRI in patients with suspected peripheral bone infection	5
13	Three-phase bone scintigraphy is a sensitive technique in patients suspected for peripheral bone infection although not highly specific	2
14	White blood cell scintigraphy and anti-granulocyte antibody scintigraphy have similar high diagnostic accuracy for diagnosis of peripheral bone infection	2
15	Pre-test probability of infection should be considered for choosing between three-phase bone scan and white blood cell scintigraphy (fractures, recent surgery, osteosynthesis, highly positive serological tests)	5
16a	^{18}F-FDG-PET has high diagnostic accuracy in peripheral bone infection without fracture and osteosynthesis	2
16b	White blood cell scintigraphy is the preferred nuclear medicine imaging technique of choice in patients suspected of peripheral bone infection with recent fracture of hardware in situ	2
17	Hybrid SPECT-CT white blood cell imaging can be performed for exact localization of infection site	2
18	When having a suspicion for hematogenous spread of the infection, ^{18}F-FDG-PET/CT is the first imaging modality of choice	5

Source: reference [16]

CT, computed tomography; *MRI*, magnetic resonance imaging; *^{18}F-FDG-PET*, ^{18}F-fluorodeoxyglucose-positron emitting tomography; *SPECT*, single-photon emission computed tomography

Three-phase bone scintigraphy is the most classic modality used in the skeletal system, with high sensitivity but low specificity in PBI [42–46]. Notably, the three phases can also be positive because of other reasons, such as post-traumatic edema, fracture healing, or recent surgery, thus explaining the low specificity especially after recent surgery. Single-photon emitting computed tomography (SPECT)/CT can be added in the late phase to improve localization of osteoblastic activity [47–54]. WBC and anti-granulocyte antibody (AGA) scintigraphy have been reported having a high diagnostic performance in PBI [45, 55–67]. However, since acquisition parameters and interpretation criteria differ between studies, there is a wide range in sensitivity and specificity. More recent WBC studies following the correct protocols show high diagnostic accuracies. Based on clinical practice, pre-test probability of infection (i.e., the probability of a patient having PBI before a diagnostic test result is known) should be considered when there is the option to choose between three-phase bone scan and WBC scintigraphy. Since in the "violated" bone there is evidence of high sensitivity of three-phase bone scan, this should be reserved to patients in whom infection probability is low. Conversely, WBC scintigraphy should be regarded as the preferred nuclear medicine modality after fracture, surgery, or when a metallic implant is present. ^{18}F-fluorodeoxyglucose-positron-emitting tomography (FDG-PET) is a promising and accurate method in PBI without implanted hardware, although there is not enough evidence to propose it as reference standard, particularly in the acute phase [5, 42, 62, 64, 68–73]. Similarly, although evidence is absent and based on clinical practice, ^{18}F-FDG-PET/CT can be used when hematogenous dissemination in patients with PBI is suspected.

Diagnosis of PJI

When early PJI is suspected, local swelling, redness, pain, and pus discharge from the wound are the most commons signs

and symptoms, particularly located over the surgical accession. In later stages and in subacute or chronic phases, inflammatory signs may be absent. Pain and loss of function may be the only symptoms, which are almost impossible to differentiate from those caused by aseptic loosening [12–15, 74].

Statements

Full list of statements regarding PJI and their evidence levels is reported in Table 2.

- Clinical and laboratory parameters (statements no. 1 to no. 4, no. 7 to no. 12)

No specific study addresses the fact that sinus tracts with purulent discharge are signs of PJI. Thus, all patients with clinical suspicion of PJI should be ruled out for infection [63, 75–80]. CRP and ESR blood tests have variable diagnostic performance (sensitivity 21–100% and 58–97%; specificity 20–96% and 33–91%, respectively) in PJI. However, being quick and inexpensive, these tests should always be per-

Table 2 Statements on the diagnosis of prosthetic joint infection

Item	Statement	Level of evidence
1	Prosthetic joint infection should be suspected when one or more of the following symptoms and signs are present: otherwise unexplained pain and/or fever, redness, swelling, scar inflammation, and movement limitations. These symptoms are (especially in the chronic phase) not specific and require other investigations	4
2	Sinus tract and purulent discharge are clear signs of prosthetic joint infection	5
3	C-reactive protein and erythrocyte sedimentation rate should always be performed in patients suspected of prosthetic joint infection. A normal value does not rule out a prosthetic joint infection	2
4	In case of fever, blood cultures should always be performed in patients suspected to have prosthetic joint infection to identify the causative bacteria	5
5	Conventional radiographies are the first imaging modality to perform in patients with suspicion of prosthetic joint infection for diagnosis and follow-up	2
6	Ultrasound can detect complications around the prosthesis, but capability of detecting infection is controversial	2
7	Imaging guidance may be useful to guide joint aspiration or periprosthetic tissue biopsy	2
8	Leukocyte counts and differential of synovial fluid have high diagnostic accuracy to detect prosthetic joint infection	2
9	Bacterial culture from joint aspiration has high diagnostic accuracy to detect prosthetic joint infection	2
10	Measurement of the synovial biomarkers alpha-defensin, leukocyte esterase, interleukin-6, and C-reactive protein is useful in the detection of prosthetic joint infection	2
11	Biopsy of peri-prosthetic tissue for histology and cultures can be performed for pre-operative diagnosis in case erythrocyte sedimentation rate and/or C-reactive protein are positive and aspiration is inconclusive or impossible to test (dry tap)	2
12	Antibiotic therapy should be postponed or discontinued before pre- and intra-operative sampling	4
13	Antibiotic therapy should not be discontinued before white blood cell scintigraphy	4
14	CT can be effectively used to diagnose prosthetic joint infection	2
15	The diagnostic accuracy for 3-phase bone scintigraphy in patients with suspected infection within the first 2 years after hip or knee prosthesis placement is low	2
16	In case of negative 3-phase bone scintigraphy, the diagnosis of prosthetic joint infection can be excluded	2
17	In case of positive 3-phase bone scan, the addition of white blood cell scintigraphy leads to high diagnostic accuracy for prosthetic joint infection	2
18	In case of negative white blood cell scintigraphy, the probability of prosthetic joint infection is low	2
19	^{18}F-FDG-PET in patients suspected of prosthetic joint infection has high sensitivity but lower specificity than white blood cell scintigraphy or anti-granulocyte antibodies scintigraphy	2
20	Anti-granulocyte scintigraphy is a good alternative to white blood cell scintigraphy with similar sensitivity and specificity	2
21	Hybrid SPECT/CT imaging can improve localization of infection (and diagnostic accuracy)	2
22	Semi-quantitative analysis of white blood cell accumulation over time in white blood cell scan increases diagnostic accuracy for prosthetic joint infection	3
23	Combining white blood cell scan with bone marrow scan increases diagnostic accuracy for prosthetic joint infection detection	2
24	MRI is fully feasible in patients with suspicion of prosthetic joint infection	2
25	MRI has high diagnostic performance in detecting prosthetic joint infection when clinically suspected with no ionizing radiations	2

Source: reference [17]

CT, computed tomography; *MRI*, magnetic resonance imaging; *^{18}F-FDG-PET*, ^{18}F-fluorodeoxyglucose-positron emitting tomography; *SPECT*, single-photon emission computed tomography

formed when PJI is suspected, using a threshold of 10 mg/l for CRP and 30 mm/h for ESR. The combination of the two markers seems to be even more reliable [81–85], although low CRP and ESR do not exclude PJI. No evidence suggests that blood culture is helpful in patients with fever and suspected PJI. However, when there is suspicion of hematogenous origin of PJI, blood culture might help.

Joint fluid aspiration has been traditionally used to rule out PJI, if there is enough fluid to aspirate. Different biomarkers can be tested. WBC count has 36–100% sensitivity and 80–99% specificity at a suggested threshold > 3000 cells/μl. Differential count has 84–100% sensitivity and 80–99% specificity at neutrophil percentage > 70% [79, 86–98]. Alpha defensin has 95.5–100% sensitivity and 95–100% specificity [89, 99–103] and seems not to be influenced by antibiotic treatment, while interleukin-6 has 62.5–97% sensitivity and 85.7–100% specificity [91, 103–107], although they are both expensive and not widely available tests. Leukocyte esterase has 66–100% sensitivity and 77–100% specificity [108–112]. Synovial CRP has 70–97.3% sensitivity and 78.6–100% specificity [89, 92, 103, 107, 113–116]. Bacterial culture has 43.5–100% sensitivity and 81.2–100% specificity [88, 93, 95, 104, 117–133]. Most authors recommend an incubation period ranging between 7 and 14 days, with at least five culture samples to confirm positivity [134]. Bacterial culture is limited by previous or ongoing antimicrobial therapy, which should be discontinued at least 2 weeks before sampling [96, 135–137].

In case of little or no fluid in the joint space, aspiration may be impossible ("dry tap"). Thus, biopsy of synovial tissue can be performed. This procedure is slightly more invasive than simple aspiration, with 79.1–100% sensitivity and 90–100% [105, 114, 138–141]. Blind procedures may lead to increased complications and lower success rate; thus, ultrasound guidance is highly recommended [141]. Ultrasound-guided aspiration has 67–69% sensitivity and 66–94% specificity [117, 142], while CT-guided aspiration has about 70% sensitivity and 100% specificity [143].

- Radiological imaging techniques (statements no. 5, no. 6, no. 14, no. 24, no. 25)

Conventional radiographs are the first imaging modality to perform in patients with suspected PJI, as they can evaluate bony structure around the implants, potentially showing the presence of abnormal findings, and being able to detect other causes of pain. As conventional radiographs become positive only when at least 30–50% of bone mass has been lost, about half of radiographs performed on infected implants are normal. Serial radiographs have 14% sensitivity and 70% specificity in PJI. The presence of gas bubbles and immature, active periostitis are highly specific signs for PJI, while implant loosening, soft tissue swelling, and periprosthetic lucency have low specificity [144–146].

Ultrasound can show synovial hypertrophy and fluid around the implant, but its ability in detecting an infection is controversial [147, 148]. In the hip, a capsule-to-bone distance > 4 mm has been reported to be 100% sensitive and 74% specific, being 100% specific when the capsule-to-bone distance is over 3.2 mm and extra-capsular fluid is seen [149]. However, others reported that anterior distension of hip capsule is not predictive of infection [150].

PJI can be also ruled out using CT, which can show soft tissue collections, and distended bursae and joint spaces. When at least one soft tissue finding is used as infection criterion, CT has 100% sensitivity, 87% specificity, and 89% accuracy while it has 83% sensitivity, 96% specificity, and 94% accuracy when joint distention is used as infection criterion [151]. A 100% positive predictive value is assigned to the presence of fluid collections in perimuscular fat and muscle bellies, while 96% negative predictive value is assigned to absence of joint effusion. Periosteal reaction is 100% specific but only 16% sensitive for PJI [152, 153]. However, these figures are valid when these signs are present, but overall accuracy of CT is generally lower than that of MRI.

Joint implants are not a contraindication to MR examinations as signal distortion is generally limited to the area of prosthesis itself [154–156]. Regarding diagnostic performance of MRI in the detection of PJI, 65–92% sensitivity and 85–99% specificity have been reported in the knee, while these figures increase to 94% sensitivity and 97% specificity in the hip [157–160]. Notably, MRI (together with ultrasound) is a modality which does not involve ionizing radiation and may be preferred when possible.

- Nuclear medicine imaging techniques (statements no. 13, no. 15 to no. 23)

Three-phase bone scintigraphy is very sensitive to any bony remodeling. When a joint is replaced, remodeling may proceed for a couple of years. A single study investigated this issue, showing that at 21 months after surgery, three-phase bone scintigraphy had 50% sensitivity and 71% specificity, concluding that this examination should be avoided in the first years after surgery [161]. However, the great advantage of three-phase bone scan is that a negative examination allows excluding the diagnosis of PJI [162–170].

When three-phase bone scan is positive, two studies reported that the addition of WBC scintigraphy may

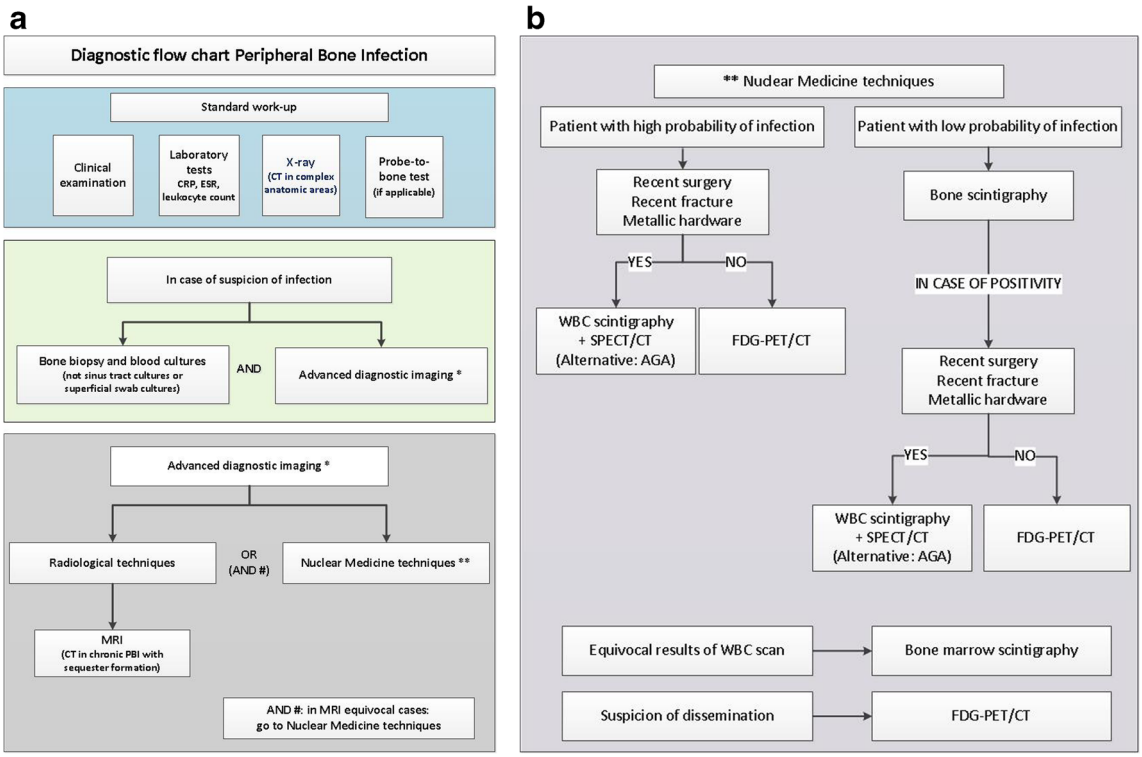

Fig. 1 **a** Proposed diagnostic flowchart based on published evidence to undertake when peripheral bone infection is suspected. Clearly, not all steps may be required in all cases and some steps may be repeated if necessary. Serological tests can be performed over time since the trend to increase or decrease is more important than a single value. At present, there is not enough clinical evidence to support the use of one advanced diagnostic imaging technique above the other. There is a lack of studies with large numbers of patients and there are hardly no comparative studies. Thus, the choice of which test to use first depends on several factors, such as the benefit for the patient, local experience, costs, and availability. In many hospitals, magnetic resonance imaging is considered as first advanced imaging modality in daily practice, mainly because of no radiation involved. In patients with metallic hardware, however, there is sufficient literature to support a preferential use of white blood cell scintigraphy. **b** Suggested path to undertake when nuclear medicine techniques are considered in the suspicion of peripheral bone infection, based on literature evidence and expert opinion. Images are reproduced from reference [16] under creative common license

increase specificity [162, 171]. With this association, they found 80% sensitivity and 99.5% specificity for PJI. Within the first years after surgery, three-phase bone scan may be avoided since it will be for sure positive due to bone remodeling and WBC scintigraphy can be used as first nuclear imaging modality. Regarding the issue of suspending antibiotic therapy before WBC scintigraphy, no study addresses specifically this issue. However, studies on antibiotic discontinuation in PBI showed no accuracy difference between the two options [172–174]. If WBC scintigraphy is negative, the diagnosis of PJI is unlikely, with negative predictive values ranging from 92% using ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO)-labeled leukocytes [175] to 100% using sulesumab (AGA) [175]. In addition to conventional qualitative evaluation, semi-quantitative analysis of WBC accumulation at 3–4 h and 20–24 h after leukocyte injection can be performed. Quantification is expressed as a ratio between radioactivity in the region of interest over background radioactivity. If ratio increases over time, WBC accumulation is reported as active and is interpreted as PJI. Conversely, a ratio decreasing over time suggests a non-infectious inflammatory process [167, 176]. The combination of WBC scintigraphy with bone marrow scintigraphy has been reported to increase the detection of PJI, being able to reduce false-positive cases particularly in doubtful cases at WBC scintigraphy. The correct interpretation criteria to be used have also been recently published by the EANM [177]. The combination of those modalities has been reported having accuracy ranging from 83 to 98% for both ^{99m}Tc-HMPAO-WBC and ^{111}In-oxine-WBC for both knee and hip PJI [168, 178–185]. A valid alternative to WBC scintigraphy is represented by AGA scintigraphy. Two meta-analyses showed that AGA scintigraphy has 83% sensitivity and 79–80% specificity in the diagnosis of PJI [186, 187], which is comparable to those of WBC scintigraphy. The

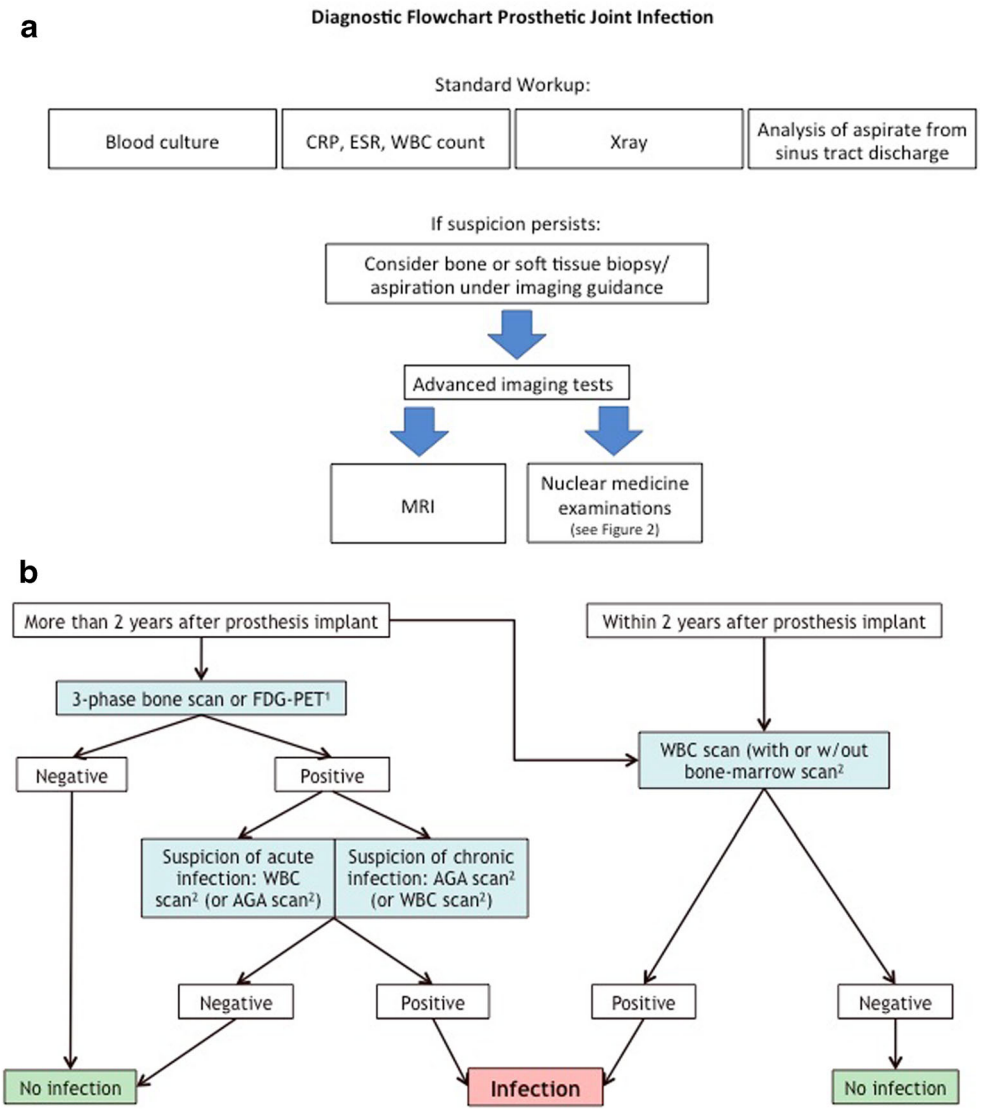

Fig. 2 **a** Proposed diagnostic flowchart based on published evidence to undertake when prosthetic joint infection is suspected. Some tests can be repeated (i.e., blood cultures, bone biopsies, or soft tissue biopsies) when needed. Serological tests (C-reactive protein, white blood cell count with differential, and erythrocyte sedimentation rate) should be performed over time since the trend to increase or decrease is more important than a single value. The choice of which test to use first depends on several factors, such as the benefit for the patient, local experience, costs, and availability. **b** Suggested path to undertake when nuclear medicine techniques are considered in the suspicion of prosthetic joint infection, based on literature evidence and expert opinion. Initial stratification is based on time after implant (more/less than 2 years). Images are reproduced from reference [17] under creative common license

comparison between ^{99m}Tc-WBC and ^{99m}Tc-besilesomab in peripheral osteomyelitis and PJI revealed no differences [56, 68, 188]. Although current recommendations on WBC scintigraphy include planar image evaluation only, the introduction of SPECT/CT has represented a remarkable advancement. Three studies showed accuracy increased up to 38% in patients with PJI [68, 174, 189]. Thus, in cases of positive WBC scintigraphy, SPECT/CT scan may provide additional information.

Few studies compared ^{18}F-FDG-PET directly to WBC and/or AGA scintigraphy [179, 190–192]. Overall, the comparison showed that ^{18}F-FDG-PET has higher sensitivity but lower specificity when PJI is suspected. However, the wide ranges of reported sensitivities (28–91%) and specificities (34–97%) are justified by different study designs and interpretation criteria. Thus, higher standardization is warranted to increase homogeneity.

Concerns on the use of ionizing radiations

Details on these aspects are presented in the original works [16–19, 193–196] and provided as Supplementary Material.

Conclusions

Overall, WBC scintigraphy and MRI have demonstrated individually the highest diagnostic performance over the other imaging modalities in the diagnosis of both PBI and PJI. However, the, the choice of which test to use first depends on several factors, such as the benefit for the patient, local experience, costs, and availability.

Figures 1 and 2 summarize the proposed diagnostic flowcharts based on published evidence and the suggested paths to

undertake when nuclear medicine techniques are considered in the suspicion of PBI and PJI, respectively.

Concluding, these flowcharts represent the first evidence, PICO-based proposals to be applied when PBI and PJI are suspected. However, since robust, comparative studies among most tests do not exist, these flowcharts also involve expert opinion based on broad consensus of multiple experts involved on these topics.

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