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

Peripheral bone infection (PBI) and prosthetic joint infection (PJI) represent two different ~~inflammatory~~ 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 launched by the the European Association of Nuclear Medicine (EANM), the European Society of Radiology (ESR), the European Society of Bone and Joint Society (EBJIS) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). The purpose of this paper is to provide an overview on the two consensus documents on PBI and PJI that originated by the conjoined work of the EANM, ESR and EBJIS (with ESCMID endorsement). After extensive literature search and following the indications of the Oxford Center for Evidence-Based Medicine, 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. From this work, authors concluded that there is ~~a clear~~ superiority of ~~W~~white ~~-~~blood ~~-~~cell scintigraphy and MRI over other imaging modalities, both for PBI and PJI. 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 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 ~~physicians~~ experts involved in these topics.

Keywords

peripheral bone infection; prosthetic bone infection; laboratory test; biopsy; imaging; nuclear medicine

Keypoints

- For peripheral bone infection and prosthetic joint infection, white blood cell scintigraphy and MRI show ~~there is no one single diagnostic method clearly~~ superiority over ~~the~~ others ~~existing~~ imaging techniques
- Two evidence- and expert-based diagnostic flowcharts involving variable combination of laboratory tests, biopsy methods, 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

Abbreviations

PBI = peripheral bone infection
PJI = prosthesis joint infection
ESR = European Society of Radiology
EANM = European Society of Nuclear Medicine
EBJIS = European Society of Bone and Joint Society
ESCMID = European Society of Clinical Microbiology and Infectious Diseases
PICO = population/problem, intervention/indicator, comparator, outcome
OCEBM = Oxford Center for Evidence-based Medicine
CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
WBC = white blood cell
CT = computed tomography
MRI = magnetic resonance imaging
SPECT = single-photon emitting computed tomography
AGA = anti-granulocyte antibody
FDG-PET = ^{18}F-fluorodeoxyglucose-positron-~~emitting~~ emission tomography
HMPAO = hexamethylpropylene amine oxime

Introduction

Peripheral bone infection (PBI) and prosthetic joint infection (PJI) represent two different ~~inflammatory~~ infectious conditions of the musculoskeletal system.

PBI include osteitis and osteomyelitis. The former refers to a bacterial infection of the periosteum, which can develop acutely (<8 weeks) or chronically (>8 weeks) after trauma or surgery; the latter refers to an infection of the medullary cavity, mainly with hematogenous origin, which lately spreads to the surrounding cortical bone. Osteomyelitis can be classified into acute or chronic, too. In the acute phase, necrotic bone and bacteria are detected concurrently. Progression to chronic osteomyelitis is characterized by the presence of avascular bony fragments, defined as *sequestra*. A strong periostal reaction usually develops around the infection, associated or not with the presence of a sinus tract. Incidence of PBI is low, accounting for about 2%~~/~~ per year in developed countries, although this figure may slightly increase after surgery (2%-4%), or trauma surgery with potentially contaminated fracture (19%), or in immunocompromised hosts.

PJI is a worrisome complication of all joint replacements. Its incidence ranges from 2% to 2.4% for newly implanted prostheses, while it may reach up to 20% for revision procedures. Due to the aging of general population, the number of replaced joints is rapidly increasing over time. Thus, PJI may represent a non-negligible health issue, leading to repeated surgery, prolonged hospitalization, increased morbidity, and increased costs. PJI can be differentiated according to its onset after surgery as early (within three months from surgery), delayed (between three months and two years), and late (over two years). While early PJI may be usually easier to recognize, as it shows the typical signs of infection, delayed and late PJI may present with a quite insidious onset and nonspecific symptoms.

When dealing with PBI and PJI, no single routine test alone can diagnose the infection 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. Regarding PJI, literature is certainly richer, however many recommendations still lack multidisciplinary approach, or are not updated on the most recent imaging modalities, or fail providing a possible diagnostic flowchart.

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 Society of Bone and Joint 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 ~~on~~ in the *European Journal of Nuclear Medicine and Molecular Imaging*.

The purpose of this paper 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

This project was commenced after a multimodality imaging symposium on PBI and PJI was organized at the EANM Annual Meeting in Milano in October 2012. There, the respective Societies realized that existing shared diagnostic recommendations on the two topics had limitations. Thus, the EANM involved the ESR, EBJIS, and ESCMID to start two separate common projects on PBI and PJI diagnosis guidelines with emphasis on imaging. Hence, separately for these two conditions, the

delegates met in Vienna in 2015 to draft provisional statements on the most current topics regarding PBI and PJI. Then, a thorough literature search was performed using the Pubmed/MEDLINE and Scopus databases and keywords were defined by the respective Society members according to the relevant topic discussed in each statement. References of the obtained papers were further screened for additional references to include. Search was restricted to papers including at least ten patients of at least 16 years of age. Per each statement, paper inclusion was based on a PICO (population/problem – intervention/indicator – comparator – outcome) question to search for evidence after converting the PICO question into a search strategy. This strategy is described extensively by the Oxford Centre for Evidence-based Medicine (OCEBM). All included papers were rated with a level of evidence, as recommended by OCEBM, and a final level of evidence was extrapolated in consensus among all panelists for each statement.

Diagnosis of Peripheral Bone Infections

In the acute setting, pain is the principal local symptom associated with reduced function [12]. Complete medical history should be taken, including all conditions that may favor the onset of PBI [10]. Physical examination may reveal the presence of a fistula with pus discharge, although in most cases only mild skin redness and swelling can be seen. In cases where a skin breach is present, the probe-to-bone test can be performed. This consists ~~in~~ of inserting a metallic probe in the breach trying to reach the bony surface. The concept behind this simple test is that if the probe can reach the bone, the same can be done by infectious bacteria [Lavery 2007]. 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 #1 to #4, #7, #8)

In case of clinical and imaging suspicion of PBI, additional diagnostic tests may be helpful to confirm the diagnosis. If a skin breach is present, the probe-to-bone test can be performed. ~~Although~~ Since this represents a routine practice in the diagnosis of diabetic foot infection, this ~~can~~ may be transferred to PBI but no clear evidence is published. Similarly, although based on conventional medical reasoning, there is no evidence that a fistula directing to the bone and concurrent purulent discharge represent the ~~prove~~ proof of an underlying bone infection.
Regarding blood tests, determination of C-reactive protein (CRP), eryt~~r~~hrocyte sedimentation rate (ESR), and white blood cell (WBC) counts should always be performed. In these patients, raised ESR and CRP may be present and may suggest the presence of ~~-~~an 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 [28]. A cut-off of 0.4 ng/ml of serum procalcitonin has been reported to be sensitive and specific in the diagnosis of acute osteomyelitis [29].
Regarding blood cultures, they become positive mostly in osteomyelitis of hematogenous origin. There is little evidence supporting the use of blood cultures in the diagnosis of PBI outside the spine [30].
To replace bone biopsy, the value of sinus tract and deep tissue cultures has been tested [33-35, 40], finding that this approach is inadequate to identify the correct pathogen in osteomyelitis. One paper ~~had~~ showed different results, involving two sinus tract cultures with bone contact at different times, and showing 94% diagnostic accuracy in cases with two concordant cultures with

bone contact [41]. Authors however concluded 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 [32, 37, 41]. For this reason, a good clinical practice recommendation should be that antibiotic administration should be suspended or postponed only if feasible and reasonable, being the optimal duration of this suspension still not established.

- Radiological ~~tests~~ imaging techniques (statements #5, #6, #9 to #12)

In PBI, conventional radiography is the first modality to perform, being cheap, available, uses reasonable amount of ionizing radiation, and excludes other causes of pain. However, conventional radiography becomes positive at least 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 [17, 18]. 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 [19].
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%) [31-33] in identifying a single causative microorganism after biopsy. However, another paper had low rate of positive specimens obtained by imaging-guided biopsy [37]. Superiority of open surgical biopsy has also been confirmed [34-36], which remains however a very invasive method of diagnosis.
Non-contrast magnetic resonance imaging (MRI) is pivotal in the assessment of PBI, having 88%-98% sensitivity, 70%-96% specificity, and 81%-86% accuracy [20-22]. MRI has the great advantage of evaluating the involvement of both the osseous and soft tissues compartments, being also able to differentiate infection from other mimickers, such as bone tumors. The use of intravenous Gadolinium 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. Although no specific paper addressed the issue of metallic fixation devices in patients with PBI, orthopedic implants in general do not represent a contraindication to MR examinations. They may produce some local susceptibility artefacts depending on the metallic alloy and on the orientation in respect to the magnetic field. However, technical advancements of MR sequences make the artefact mostly limited to the profile of the implant itself.

- Nuclear medicine ~~tests~~ imaging techniques (statements #13 to #18)

Three-phase bone scintigraphy is the most classic modality used in the skeletal system. It has high sensitivity but low specificity in the diagnosis of PBI [43-47]. In fact, 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 also added in the late phase to improve localization of osteoblastic activity [24, 71-77]. On the other hand, WBC and anti-granulocyte antibody (AGA) scintigraphy have been reported having a similar high diagnostic accuracy in the diagnosis of PBI [46, 48-60]. However, the acquisition modality and interpretation criteria adopted between the two techniques are not always similar, making the comparison quite difficult among different radiotracers. At any rate, based on clinical practice, pre-test probability of infection is a parameter to consider when there is the option to choose between three-phase bone scan and WBC scintigraphy. Since low sensitivity of three-phase bone scan is particularly evident in the “violated”

bone, it should be reserved to patients in whom infection probability is low. On the other hand, WBC scintigraphy should be regarded as the preferred nuclear medicine modality after fracture, surgery, or when a metallic implant is present. Regarding ^{18}F-fluorodeoxyglucose-positron-emitting tomography (FDG-PET), there is high evidence that this modality is a very promising and accurate method in PBI without implanted hardware, although there is not enough evidence to propose it yet as the reference standard, particularly in the acute phase [6, 43, 55, 57, 63-68]. Similarly, although evidence is absent and based on clinical practice, ^{18}F-FDG-PET/CT can be used when suspecting hematogeneous dissemination in patients with PBI.

Diagnosis of Prosthetic Joint Infections

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.

Statements

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

- Clinical and laboratory parameters (statements #1 to #4, #7 to #12)

Similarly to what is stated for PBI, there is no specific paper addressing the fact that sinus tracts with purulent discharge are signs of PJI. Thus, all these patients should be ruled out for infection [48-54]. In this setting, the use of CRP and ESR blood tests has variable diagnostic performance (sensitivity 21%-100% and 58%-97%; specificity 20%-96% and 33%-90.91%, respectively) in detecting PJI. However, being quick and inexpensive, these tests should ~~be~~ always be performed when PJI is suspected, taking care to use a threshold of 10 mg/l for CRP and 30 mm/hour for ESR. Using the combination of the two markers seems to be even more reliable [56, 59, 87], although low CRP and ESR do not exclude PJI. Regarding the use of blood cultures, no evidence suggests it may be helpful in patients with ~~temperature~~ fever and suspected PJI. However, when there is suspicion of hematogenous origin of PJI, blood cultures 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 of >3000 cells/µl. Differential count has 84%-100% sensitivity and 80%-99% specificity at neutrophil percentage >70% [21, 58, 60, 63, 64, 77, 78, 82-84, 97-100]. Alpha-defensin has 95.5%-100% sensitivity and 95%-100% specificity [69,120-123] and seems not to be influenced by the antibiotic treatment, while interleukin-6 has 62.5%-97% sensitivity and 85.7%-100% specificity [57, 77, 81, 123, 129, 130], although they are both expensive and not widely available tests. Leukocyte esterase has 66%-100% sensitivity and 77%-100% specificity [124-128]. Synovial CRP has 70%-97~~.3~~% sensitivity and 7~~8.6~~9-100% specificity [78, 80, 85, 121, 123, 130-132]. Bacterial culture has 4~~3.5~~4%-100% sensitivity and 81~~.2~~%-100% specificity [60, 79, 82, 84, 96, 101-118]. Most authors recommend an incubation period ranging between 7 and 14 days, with at least five samples to confirm positivity. Bacterial culture is limited by previous or ongoing antimicrobial therapy, which should be discontinued at least two weeks before sampling [20, 97, 136, 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% [67, 68, 133-135]. Blind procedures may lead to increased complications (such as neurovascular damages) and lower rate of success, thus

the use of ultrasound guidance is highly recommended [ref]. Ultrasound-guided aspiration has 67%-69% sensitivity and 66%-94% specificity, [94, 95] while CT-guided aspiration has around 70% sensitivity and 100% specificity [96].

- Radiological ~~tests~~ imaging techniques (statements #5, #6, #14, #24, #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 said, the main limitation is that conventional radiographs become positive only when at least 30%-50% of bone mass has been lost, thus about half of radiographs performed on infected implants are normal. Serial radiographs have 14% sensitivity and 70% specificity in this setting. 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 [89-91].

Ultrasound can well demonstrate the presence of synovial hypertrophy and fluid around the implant, but its ability in detecting an infection is controversial. 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 [92]. However, others reported that anterior distension of hip capsule is not predictive of infection [93].

PJI can be also ruled out using CT, which is able to 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 [154]. A 100% positive predictive value is assigned to the presence of fluid collections in peri-muscular 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 [155, 156].

Joint implants are not a contraindication to MR examinations as their interaction with the magnetic field is minimal and signal distortion is generally limited to the area of prosthesis itself [200-202]. Regarding diagnostic performance of MRI in the detection of PJI, 65%-92% sensitivity and 85%-99% specificity has been reported in the knee, while these figures increase to 94% sensitivity and 97% specificity in the hip. Notably, MRI (together with ultrasound) is a modality which does not involve ionizing radiation. This should be carefully considered especially in patients needing multiple examinations over time.

Met opmerkingen [M1]: Can be misleading. Don't you think we should add that overall the diagnostic accuracy of CT is lower than that reported for MRI?
AG: yes agree, it is 100% when these fluid collections are present, but if they are not? Then accuracy is much lower I guess?

- Nuclear medicine ~~tests~~ imaging techniques (statements #13, #15 to #23)

Three-phase bone scintigraphy is very sensitive to any bony remodelling. When a joint is replaced, remodelling may proceed for ~~up one~~a couple of years. A single paper 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 [157]. 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 papers reported that the addition of WBC scintigraphy may increase specificity [162, 165]. 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 remodelling and WBC scintigraphy can be used as first nuclear imaging modality. Regarding the issue of suspending or not antibiotic therapy before WBC scintigraphy, there is no paper addressing specifically this issue, so no real conclusion can be drawn. However, papers on antibiotic discontinuation in PBI showed no accuracy difference between the two options [142-144]. Overall, 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 [176] to 100% using sulesumab (AGA) [178]. In addition to conventional qualitative evaluation, semi-quantitative analysis of WBC accumulation at 3-4 hours and 20-24 hours 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, 191]. 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 (ref: Signore A, Jamar F, Israel O, Buscombe J, Martin-Comin J, Lazzeri E. Clinical indications, image acquisition and data interpretation for white blood cells and anti-granulocyte monoclonal antibody scintigraphy: an EANM procedural guideline. Eur J Nucl Med Mol Imaging. 2018 Sep;45(10):1816-1831). The combination of those modalities has been reported having ~~accuracy~~ accuracies ranging from 83% to 98% for both ^{99m}Tc-HMPAO-WBC and ^{111}In-oxine-WBC for both knee and hip PJI [31, 34, 168, 180, 194-198]. 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 comparison between ^{99m}Tc-WBC and ^{99m}Tc-besilesomab in peripheral osteomyelitis and PJI revealed equivalent results of the two modalities [178, 184, 185]. Although current recommendations on WBC scintigraphy include only evaluation of planar images, the introduction of hybrid imaging, such as SPECT/CT, has represented a remarkable advancement. Three papers showed accuracy increased up to 38% in patients with PJI [176, 188, 189]. Thus, in cases of positive WBC scintigraphy, SPECT/CT scan ~~may~~ provide additional information of the exact location of the infection and ~~may be~~is recommended.

Few papers compared ^{18}F-FDG-PET directly to WBC and/or AGA scintigraphy [34, 182, 183]. 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

Ionizing radiations are commonly used in radiological and nuclear medicine examinations and are considered a potential risk for patients. The European Union has recently issued the new 2013/59/EURATOM directive, laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation [https://ec.europa.eu/energy/sites/ener/files/documents/CELEX-32013L0059-EN-TXT.pdf]. In 2014, the ESR launched the EuroSafe Imaging Campaign [http://www.eurosafeimaging.org/] to promote quality and safety in medical imaging. The mission of EuroSafe Imaging is to support and strengthen medical radiation protection across Europe. The EANM has similarly promoted this topic through educational programs directed to both physicians and radiographers [https://www.eanm.org/content-eanm/uploads/2016/12/EANM_2016-TG_RadiationProtection_lowres.pdf].

Overall, the principle of justification when using ionizing radiation for medical imaging should be always kept at the centre of the diagnostic path of each patient. Every physician must always consider potential benefits, risks, and costs of medical exposure and should always consider the use of non-radiating imaging modalities which provide comparable diagnostic results. This is

particularly true when a clear evidence of superiority of a radiating over a non-radiating modality is missing, as it happens in most cases discussed in the present consensus document.

Conclusions

From what is reported above, a ~~clear~~ superiority of ~~white blood cell~~WBC scintigraphy and MRI over the other imaging modalities can be established, both for PBI and PJI. However, 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 Figures 1 and 2, we report the proposed diagnostic flowcharts based on published evidence so far and the suggested paths to undertake when nuclear medicine techniques are considered in the suspicion of PBI and PJI, respectively. In conclusion, 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 ~~physicians~~ experts involved on these topics.

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Tables

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 work-up; 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 haematogenous spread of the infection, ^{18}F-FDG-PET/CT is the first imaging modality of choice.	5

Note.- Source reference #xx. CT, computed tomography; MRI, magnetic resonance imaging; ^{18}F-FDG-PET, 18F-fluorodeoxyglucose-positron emitting tomography; SPECT, single-photon emitting computed tomography.

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-	2

	granulocyte antibodies scintigraphy.	
20	Anti-granulocyte scintigraphy is a good alternative to white blood cells 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

Note.- Source reference #xx. CT, computed tomography; MRI, magnetic resonance imaging; ^{18}F-FDG-PET, 18F-fluorodeoxyglucose-positron emitting tomography; SPECT, single-photon emitting computed tomography.

Figure legends

Figure 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. Both figures are reproduced with permission from reference #xx.

Figure 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). Both figures are reproduced with permission from reference #xx.