Imaging of osteomyelitis: the key is in the combination

An accurate diagnosis of osteomyelitis requires the combination of anatomical and functional imaging techniques. Conventional radiography is the first imaging modality to begin with, as it provides an overview of both the anatomy and the pathologic conditions of the bone. Sonography is most useful in the diagnosis of fluid collections, periosteal involvement and soft tissue abnormalities, and may provide guidance for diagnostic or therapeutic interventions. MRI highlights sites with tissue edema and increased regional perfusion, and provides accurate information of the extent of the infectious process and the tissues involved. To detect osteomyelitis before anatomical changes are present, functional imaging could have some advantages over anatomical imaging. Fluorine-18 fluorodeoxyglucose-PET has the highest diagnostic accuracy for confirming or excluding the diagnosis of chronic osteomyelitis. For both SPECT and PET, specificity improves considerably when the scintigraphic images are fused with computed tomography. Close cooperation between clinicians and imagers remains the key to early and adequate diagnosis when osteomyelitis is suspected or evaluated.

Osteomyelitis is inflammation of the bone that is usually due to infection. There are different classification systems to categorize osteomyelitis. Traditionally, it has been labeled as acute, subacute or chronic, depending on its clinical course, histologic findings and disease duration, but there is no consensual agreement on the temporal scale used or specific findings. As a result, some researchers have proposed more detailed classification systems, such as the Waldvogel classification system based on etiology of the infection (hematogenous spread of an organism, direct inoculation of an organism through trauma or contiguous spread from a soft tissue infection), and Cierny-Mader classification, a descriptive system that takes into account both anatomic factors and the host’s physiologic status [1,2].

An inadequate or late diagnosis increases the degree of complications and morbidity; for these reasons, imaging techniques are essential to confirm the presumed clinical diagnosis and to provide information regarding the exact site and extent of the infection process [1].

Although a variety of diagnostic imaging techniques is available for excluding or confirming osteomyelitis, it is often difficult to choose the most appropriate technique to conclusively establish the diagnosis of osteomyelitis. Several imaging modalities have been used in the evaluation of suspected osteomyelitis. The ideal imaging technique should have a high sensitivity and specificity; numerous studies have been published concerning the accuracy of the various modalities in diagnosing chronic osteomyelitis [2–4]. Confirmation of the presence of osteomyelitis usually entails a combination of imaging techniques. Table 1 shows the main pathologic findings of osteomyelitis assessed by diverse imaging techniques.

### Conventional radiography

Plain films are usually the first imaging test ordered by clinicians [5]. Conventional radiography should not be used to exclude acute osteomyelitis in a patient who has experienced symptoms for less than 10 days. Nevertheless, deep soft tissue swelling, joint effusion or early periosteal changes may be seen within days after onset of infection. Furthermore, conventional radiography helps to exclude fracture or tumor.

Destructive bone changes do not occur until 7–10 days after the onset of infection. During the first 2–3 days of symptoms, radionuclide bone imaging may be particularly useful in showing a well-defined focus of increased uptake on the dynamic perfusion, as well as early blood pool and delayed images corresponding to the area of hyperemia [6]. At this early stage, the main utility of plain film is to provide a global view of the bone marrow and to confirm the presence of osteomyelitis.
Imaging of osteomyelitis: the key is in the combination of the suspect part of the skeleton and to provide information regarding differential diagnosis in a patient complaining of pain. Structural bony changes and periosteal reaction consist first of subperiosteal resorption or scalloping, which creates radiolucencies within cortical bone that may progress to irregular destruction with areas of periosteal new bone formation. However, hematogenous osteomyelitis in children typically arises within cancellous bone, mostly in the vicinity of physeal plates, and secondarily involves cortical bone and periosteum.

In general, osteopenia becomes evident on conventional radiographs after the loss of approximately 30–50% of bone mineralization. Follow-up radiographs may be normal if therapy is successful, or in some instances periosteal new bone formation may be apparent. The search for sequestra is a common and important diagnostic challenge in chronic osteomyelitis. The presence of a sequestrum may lead to a decision of surgery. A bone sequestrum manifests on conventional radiographs as a piece of calcified tissue within a lucent lesion. The increased density of the sequestrum relative to the surrounding bone is a consequence of its absence of blood supply. As a result of this devascularization, the sequestrum does not participate in the reactive hyperemia and therefore does not exhibit the osteopenia of the adjacent living bone. A wide scope of bone lesions may present with an image suggestive of sequestrum including osteoid osteoma, eosinophilic granuloma and primary lymphoma [7].

A lucent circumscribed lesion (Brodie’s abscess) in the metaphyses of long bones predominantly abutting the growth plate with well-defined dense margins is commonly seen in the tibia and femur of children with subacute osteomyelitis. Periostitis, involucrum formation and sinus tracts are due to a subperiosteal abscess with lifting of the periosteum, new bone formation and soft tissue fistulas. All of these findings are indicative of the protracted nature of the infection process.

Table 1. Imaging abnormalities in osteomyelitis.

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<td></td>
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<td></td>
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of the diabetic foot

In a recent meta-analysis of the accuracy of diagnostic tests for osteomyelitis in diabetic patients with foot ulcers, the sensitivity of plain radiography for diagnosis of osteomyelitis was highly variable, ranging from 0.28 to 0.75. The wide variation may be attributable to the timing of performance of the radiograph in relation to the chronicity of the ulcer. The pooled sensitivity was 0.54 and the pooled specificity was 0.68. The diagnostic odds ratio...
Imaging of osteomyelitis: the key is in the combination of therapy. In this technique, a small flexible catheter is placed within a cutaneous opening. Retrograde injection of contrast material defines the course and extent of the sinus tract and its possible communications with neighboring structures. Sinography or fistulography may be combined with CT for better delineation of the anatomical relationships of the contrast-filled track [8]. Sinography is not widely used in clinical practice.

**Ultrasonography**

During recent years, ultrasonography has had an expanding role in the investigation of infectious processes of the soft tissues and in early detection of subperiosteal fluid collections that are seen in acute osteomyelitis in childhood [11].

A constellation of grayscale and color Doppler ultrasound findings can be highly indicative of bone infection including: fistulous tracts, periosteal thickening, cortical discontinuity, soft tissue abscess and cellulitis, juxta-cortical fluid collections, distension of the pseudocapsule in arthroplasties and periosteal vasculularity in patients with long-standing chronic post-traumatic/postoperative osteomyelitis [12]. The presence of joint effusion may be a diagnostic clue to the existence of septic arthritis.

Power Doppler ultrasonography detects the increased microvascular flow associated with infectious collections [13]. Furthermore, ultrasonography has been demonstrated to be useful in assessing therapeutic response and as a guide for accurate aspiration of material for culture [14–16].

**MRI**

MRI provides excellent delineation between bone and soft tissue as well as abnormal and normal bone marrow. Furthermore, it can detect osteomyelitis as early as 3–5 days after infection. MRI is used to evaluate the extent of abnormalities and in cases of surgical treatment, it is valuable for planning an accurate surgical strategy or clinical follow-up [8].

MRI helps to detect early stages of osteomyelitis owing to its ability to identify bone and soft-tissue edema. It is particularly useful for detecting osteomyelitis of the spine and pelvic bones. In addition, it is helpful for excluding complications. It may be instrumental in difficult differential diagnosis (infection vs tumor).

Disadvantages of MRI are its occasional inability to distinguish infectious from reactive inflammation and its limited resolution in areas with metallic implants, such as joint prostheses or fixation devices.

MRI has the potential to differentiate a true avascular sequestrum surrounded by necrotic tissue from a piece of residual vascularized tissue from a piece of residual vascularized...
normal bone. Nonenhanced and gadolinium-enhanced MRI sequences are required to fully characterize a sequestrum in chronic osteomyelitis [7].

The typical appearance of acute osteomyelitis in an MRI scan is a localized area of abnormal bone marrow with decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images [17].

\textbf{Special situations}

\textbf{Diabetic foot}

One devastating complication in diabetic patients is foot osteomyelitis; early diagnosis is required in order to give adequate treatment. Recently, a meta-analysis examined the accuracy of MRI as a diagnostic test in patients with diabetic foot ulcers and osteomyelitis; the authors found the pooled sensitivity was 0.90 (95% CI: 0.82–0.95) and the pooled specificity was 0.79 (95% CI: 0.62–0.91). The diagnostic OR was 24.36. The measurement of accuracy was the highest among all of the diagnostic tests that were studied [5,18].

\textbf{Vertebral osteomyelitis}

In those patients with neurologic impairment, MRI should be the first diagnostic step, to look for spinal epidural abscess and to rule out a herniated disk. MRI has a high accuracy (90%) for diagnosing spinal osteomyelitis [19,20].

In a different scenario, the differential diagnosis between intervertebral degenerative osteochondrosis and septic discitis is difficult. In degenerative disk-related inflammatory end plates, the magnetic resonance pattern of bone marrow edema, including low signal on T1-weighted and high signal on T2-weighted images, reflects the development of a highly vascular fibrous tissue inside end-plate bone marrow. Similarly, infected tissue presents increased vascularity reflected by substantial enhancement on gadolinium-enhanced T1-weighted sequences. Gadolinium contrast agents, as markers of the extracellular space, induce pronounced enhancement of tissues, presenting increased vascularity, and are therefore not specific to infection or sterile inflammation.
No text provided
limited spatial resolution, low specificity, physiological bowel excretion and the high radiation dose [23].

Gallium scans may reveal abnormal accumulation in patients who have active osteomyelitis when technetium scans reveal decreased activity (‘cold’ lesions) or perhaps normal activity. $^{67}$Ga-citrate has been used with reasonable sensitivity (73%) and relatively low specificity (61%). $^{67}$Ga-citrate is now less frequently used owing to the availability of more favorable compounds and techniques [23].

- **Radiolabeled leukocytes**

White blood cell scan was performed originally with $^{111}$In-WBC and more recently with $^{99m}$Tc-hexamethylpropyleneamine oxime-labeled white cells. The principle is that the labeled WBCs concentrate in areas of inflammation, and the specificity of the study is improved to 80–90% compared with bone scans, particularly when complicating conditions are superimposed. In a review and meta-analysis, the sensitivity for extra-axial chronic osteomyelitis was 84% compared with 21% for the detection of chronic osteomyelitis in axial skeleton [3,8]. Combined $^{111}$In-WBC and bone marrow imaging with $^{99m}$Tc-sulfur colloid demonstrated a 100% sensitivity and 98% specificity in 50 patients with suspected infected total-hip arthroplasty [24].

Today, labeled leukocyte imaging is the procedure of choice for diagnosing prosthetic joint infection [25]. The main disadvantages of $^{111}$In-WBC and $^{99m}$Tc-WBC are their laborious preparation, requirement of specialized equipment, and the handling of potentially infectious blood [23].

- **Radiolabeled specific antigranulocyte monoclonal antibodies**

Considerable effort has been devoted to the search for in vivo methods of labeling leukocytes, including peptides and antigranulocyte antibodies. Radiolabeled antigranulocyte antibodies have been developed for in vivo labeling of white blood cells. Antibodies accumulate in infectious and inflammatory foci mainly by nonspecific extravasations, because of the enhanced vascular permeability in combination with specific targeting of infiltrated granulocytes. Overall sensitivity for infection detection with radiolabeled antibodies is approximately 80–90%. Peripheral bone infections are adequately visualized; however, sensitivity decreases when the infections are located near to the spine. $^{99m}$Tc-anti-CD15 IgM and $^{99m}$Tc-anti-NCA-95 IgG are some of the most effective antibodies to diagnose bone and joint infections.

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$^{67}$Ga: Gallium-67; $^{99m}$Tc: Technetium-99m; CT: Computed tomography; FDG: Fluorine-18 fluorodeoxyglucose; HDP: Hydroxymethane diphosphonate; MDP: Methylene diphosphonate; WBC: White blood cells.
Nonspecific IgG
Radiolabeled nonspecific human IgG also accumulates in infectious and inflammatory foci by nonspecific extravasation facilitated by enhanced vascular permeability [23]. \(^{111}\)In-IgG has demonstrated excellent performance in the localization of musculoskeletal infection and inflammation.

Antibodies
BW 250/183 (Granuloscint; CISBio International, Gif sur Yvette, France) is a murine monoclonal IgG1 immunoglobulin that binds to the nonspecific cross-reacting antigen-95 (NCA-95) present on leukocytes. Sensitivity for osteomyelitis ranges from 69% in the hips to 100% for the lower leg and ankle, probably reflecting easier detection with decreasing marrow distally [19]. Today, labeled leukocyte imaging is the procedure of choice for diagnosing prosthetic joint infection [25].

Sulesomab is a 50-kDa fragment antigen-binding (Fab) portion of a murine monoclonal antibody of the IgG1 class that binds to the NCA-95 antigen on leukocytes [26]. Reported sensitivity, specificity and accuracy of the test were 90–93, 85–89 and 88–90%, respectively.

Immunoscintigraphy with \(^{99m}\)Tc-fanolesumab, a murine M-class immunoglobulin that binds to the CD15 antigen expressed on human neutrophils, eosinophils and lymphocytes. Sensitivity reaches 91% with a lower specificity of 69%; nevertheless in 2004, it was withdrawn from the US market as a result of serious reports of cardiopulmonary events [27].

Fluorine-18 fluorodeoxyglucose-PET
Fluorine-18 fluorodeoxyglucose (FDG) is transported into cells via glucose transporters, and phosphorylated by hexokinase inside the cell to form fluorodeoxyglucose-6-phosphate. The phosphorylated deoxyglucose cannot be further metabolized and, thus, FDG accumulates in activated lymphocytes, neutrophils and macrophages with minimal decrease over time. FDG therefore concentrates in sites of infection, although it is a nonspecific tracer that also accumulates in regions of aseptic inflammation, as well as in malignant lesions [28].

This technique has several potential advantages: results are available within 30–60 min of tracer administration, imaging is not affected by metallic implant artifacts, and it has a distinctly higher spatial resolution than images obtained with single photon-emitting tracers. This imaging modality is highly specific for the diagnosis of osteomyelitis in diabetic foot [18].

PET systems are relatively novel techniques that are being applied in several medical fields. It has been demonstrated that FDG-PET has the highest diagnostic accuracy for confirming or excluding the diagnosis of chronic osteomyelitis in comparison with bone scintigraphy, MRI or leukocyte scintigraphy; FDG-PET is also superior to leukocyte scintigraphy for detecting chronic osteomyelitis in the axial skeleton [18,23,29].

Nawaz et al. assessed the diagnostic performance of FDG-PET to diagnose osteomyelitis in the diabetic foot, and compared it with that of MRI and conventional radiography in 110 patients with diabetic foot disease. They found that FDG-PET had a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of 81, 93, 78, 94 and 90%, respectively; while MRI had a sensitivity, specificity, PPV, NPV and accuracy of 91, 78, 56, 97 and 81%, respectively. Conventional radiography had a sensitivity, specificity, PPV, NPV and accuracy of 63, 87, 60, 88 and 81%, respectively. They concluded that MRI is more sensitive and has the ability to provide anatomical details in addition to detecting abnormalities within the bone marrow, joint spaces and surrounding soft tissue; however, it is relatively less specific than FDG-PET. They propose to perform MRI first and if this results in a ‘positive’, then complete the follow-up of osteomyelitis in diabetic foot patients by performing FDG-PET imaging owing to its high specificity [18].

Hybrid imaging systems
It is well known that nuclear medicine images demonstrate function, rather than anatomy. Planar scintigraphy used to be the standard technique used to establish the diagnosis of osteomyelitis. However, the need for improved localization and precise definition of the infectious process extent has been facilitated by the recent development of hybrid systems (SPECT/CT and PET/CT devices), capable of performing functional and morphological images by exploiting the features of both techniques in the same scanning session. These systems allow more detailed 3D localization compared with planar imaging, and also provide useful information in both patients with osteomyelitis and in those with infected joint prostheses [23]. The process of image acquisition and fusion is of importance in accurately localizing radiopharmaceuticals, accumulation, detecting occult pathological sites, characterizing the
Ultrasound is accessible, low cost and noninvasive.

Allows identification of early soft tissue changes: fistulous tracts, fluid collections, cortical discontinuity and abscess.

Useful to define the course and extent of the sinus tract and its possible communications with neighboring structures.

Main findings include osteopenia, lytic lesions, periosteal thickening and loss of trabecular architecture.

Changes are visible after several days from the beginning of the process.

First imaging technique used to gain an overview of the anatomy and pathology of bone.

Conventional radiography still remains the first imaging modality. MRI and nuclear medicine are the most sensitive and specific methods for the detection of osteomyelitis. A CT scan can be a useful method to detect early osseous erosion and to document the presence of sequestrum, foreign body or gas formation; it is generally less sensitive than other modalities for the detection of bone infection.

MRI provides more accurate information regarding the extent of the infectious process. Ultrasound represents a noninvasive method to evaluate the involved soft tissues and cortical bone and may provide guidance for diagnostic or therapeutic interventional, drainage or tissue biopsy. PET and SPECT are highly accurate techniques for the evaluation of chronic osteomyelitis, allowing differentiation from soft tissue infection.

Future perspective

An ideal imaging technique should demonstrate functional and anatomical definition, excluding inflammatory or tumoral pathologies. Currently, there is no perfect imaging technique for the diagnosis of osteomyelitis. The hybrid imaging systems are able to acquire functional and structural data in the same scanning session and, therefore, to limit the problems often observed with software approaches for image registration and fusion. Hybrid imaging systems represent the present and future of diagnostic imaging in osteomyelitis. However, technical improvements, widespread availability and lower costs in this computer-aided imaging techniques are encouraged.

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Executive summary

**Conventional radiography**
- First imaging technique used to gain an overview of the anatomy and pathology of bone.
- Changes are visible after several days from the beginning of the process.
- Main findings include osteopenia, lytic lesions, periosteal thickening and loss of trabecular architecture.

**Sinography**
- Useful to define the course and extent of the sinus tract and its possible communications with neighboring structures.

**Ultrasonography**
- Allows identification of early soft tissue changes: fistulous tracts, fluid collections, cortical discontinuity and abscess.
- Ultrasonography is accessible, low cost and noninvasive.

**MRI**
- Provides excellent delineation between bone and soft tissue as well as abnormal and normal bone marrow. Detects osteomyelitis as early as 3–5 days after infection. Used for the evaluation of the extent of the abnormalities.

**Computed tomography**
- Provides a good definition of cortical bone abnormalities, sequestra, involucra, intraosseous gas, periosteal reaction and blurring of fat planes.

**Nuclear medicine**
- Various modalities detect osteomyelitis 10–14 days before changes are visible on plain radiographs. These techniques are highly sensitive and depending on the clinical situation have a moderate-to-high specificity.
Reviews the literature on diagnostic accuracy and clinical value of SPECT and PET for imaging of bone and joint infections.


Extensive review of labeled leukocyte imaging and possible applications.


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**Bibliography**

Papers of special note have been highlighted as:

* of interest
** of considerable interest

8. According to a meta-analysis, among the various imaging modalities available, MRI is the most accurate in diabetic patients with foot ulcers.
11. Reviews the main characteristics of the sequestrum bone imaging and describes the main features and differential diagnosis.
13. Comprehensive review article of current imaging techniques for the diagnosis of osteomyelitis.
23. Describes different scenarios of osteomyelitis in long bones.
25. In this article we can confront two new diagnosis techniques that in this moment are the more sensible and specific for an accurate diagnosis of osteomyelitis in the diabetic foot.