Eur. Radiol. 9, 894–900 (1999)

Pictorial review

Osteomyelitis: a review of currently used imaging techniques

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Received: 18 May 1998; Revision received: 6 July 1998; Accepted: 28 August 1998

Abstract. Conventional radiographs remain the initial imaging modality involved in the diagnosis of osteomyelitis. Bone scintigraphy and its specific agents did not only eliminate the problems of inherent low sensitivity of conventional radiographs, but also increased the specificity to higher degrees. Spiral CT, on the other hand, has solved several diagnostic problems, such as osteomyelitis of the sterno-clavicular junction and hidden areas in the pelvic bones. Magnetic resonance imaging with its multiplanar capability, greater anatomic details and excellent soft tissue bone marrow contrast resolution has a significant role in surgical planning and limb preservation. Ultrasound and US-guided aspiration has recently been involved in the diagnosis and management of osteomyelitis with several advantages particularly in children. Our goal in this review is to outline the ability of various imaging techniques by comparing their strengths and weaknesses in the diagnosis of osteomyelitis. Finally, we suggest various imaging algorithms for specific clinical scenarios. Spondylitis and septic arthritis are not discussed in this review.

Key words: Osteomyelitis – Radiography – Bone scintigraphy – CT – Ultrasound – MR imaging

Introduction

Osteomyelitis can be a devastating disease resulting in significant morbidity, including pain, chronically draining sinuses, loss of function, amputation and death. The diagnosis of osteomyelitis is made on the basis of clinical, laboratory and imaging examinations. This review shows that various imaging techniques involved are important and complementary, rather than competitive, in the diagnosis of osteomyelitis. It is vital to understand the limitation of each imaging modality in order to avoid any delay in the diagnosis and management and prevent possible complications.

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Clinical and laboratory evaluation

The diagnosis of osteomyelitis is usually made on the basis of clinical, laboratory, and imaging examinations. A history of past medical illness, treatment, surgeries and any physical evidence of trauma or previous surgery is valuable. Clinically, the patient with osteomyelitis complains of pain, fever, local swelling and sometimes hotness and redness at the site of infection. In rare instances osteomyelitis is discovered as an incidental finding. Certain laboratory tests, such as the white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and C-reactive Protein (CRP), may be helpful as a baseline during treatment. In children with acute osteomyelitis CRP was found to be more sensitive than ESR and WBC count in predicting the effectiveness of the therapy and recovery from osteomyelitis [1]. Furthermore, monitoring serial CRP values can alert the physician to complications and predict outcome earlier than clinical signs or roentgenograms [2]. The ESR and WBC count proved to be unreliable in chronic osteomyelitis and in monitoring response to therapy.

Imaging evaluation

Conventional radiographs

Radiographic changes in acute hematogenous osteomyelitis lag between 7 and 10 days behind the evolution of infection. The earliest changes are soft swelling and destroyed fascial planes, followed by periosteal thickening and/or elevation and osteopenia. Cortical destruction appears later as small holes which become larger coalescent lesions, and finally progress to completely involve a region of cortex. Sequestra, necrotic bone, involucra,

and cloacae opening in involucurum are infrequent findings in acute osteomyelitis. Chronic osteomyelitis demonstrates sclerotic bone and a characteristic periosteal reaction. Cloacae and sequestra appear as isolated segments of the sclerotic bone. Rarely, chronic osteomyelitis may be predominantly sclerotic, in which case it may easily be mistaken for a primary bone tumor such as osteosarcoma. Brodies's abscess appears as an eccentric lytic lesion with a well-circumscribed, sclerotic rim that is well defined on the inside and ill defined on the outside [3].

Bone scintigraphy

Bone scan

Due to radiographic lag of plain films in acute osteomyelitis, bone scan acquired an important role in the diagnosis because it can visualize osteomyelitis hours after onset of infection. Technetium 99 m (Tc 99 m) is the principal radioisotope employed in most clinical radiopharmaceuticals presently and the most widely used radionuclide agents are Tc-99 m methylene diphosphonate (Tc-MDP) and hydroxymethylene diphosphonate (Tc-HMDP). Abnormal skeletal findings on a bone scan are non-specific, and the hot lesion reflects the degree of reactive bone formation as well as increased blood flow; therefore, an intact blood supply is required. Photopenic lesions are less common but may represent osteomyelitis and are usually secondary to inadequate blood supply due to subperiosteal pus, joint effusion, soft tissue swelling or an extremely rapid, progressive and destructive process. In addition to delayed images only, a triple-phase bone scan has been used to evaluate the inflammatory process. The first phase characterizes blood flow to the area, whereas the second visualizes the blood pool. These two early phases act to evaluate the degree of inflammation and hyperemia. Classically, osteomyelitis presents as a region of increased blood flow and should appear hot also in the other two phases (Fig. 1).

Complications, such as arthritis, healing fractures, and previously treated osteomyelitis, show little abnormality on the first two phases, but may show markedly increased uptake on delayed bone images only. Often, however, it may be difficult to distinguish osteomyelitis from other entities such as diabetic osteoarthropathy, which is often abnormal in all three phases. Reported sensitivities of bone scans for the detection of osteomyelitis vary from 32 to 100 % [4, 5]. The higher sensitivity can be achieved when high-resolution images are produced in patients with uncomplicated osteomyelitis. Single photon emission computed tomography (SPECT) is such an example and it is probably more sensitive to small abnormalities due to its superior resolution. In uncompromised bone, a negative bone scan rules out osteomyelitis with an overall sensitivity of 90 % or greater. Sensitivity is perhaps somewhat lower for children and neonates as well as in the elderly with severe osteoporosis, peripheral vascular disease, and patients with metabolic bone disorders. When the bone scan is abnormal, tests that increase the low specificity of bone scans are required.

Gallium

Gallium-67 citrate was the first scintigraphic agent used to detect inflammatory process and in the work-up of fever of unknown origin. Increased uptake of gallium-67 citrate at the site of infection is attributable to in vivo labeling of serum proteins, leukocytic lysosomes, and endoplasmic reticulum along with increased vascular permeability and direct bacterial uptake [6–8]. After intravenous administration, there is prominent activity in the liver and spleen, with some uptake in the bone and hematopoietic marrow. Additional sites of normal accumulation include the salivary and lacrimal glands, breasts and external genitalia. During the first 24 h gallium-67, is primarily excreted through the kidneys; thereafter, the major route of excretion is through the gastrointestinal tract. In a typical gallium-67 study, images are acquired the next day. Earlier images may be obtained, but the target-to-background definition is much better after 24 h. It is common to acquire 48- or 72-h images to eliminate confusion with any bowel activity. It was hoped that gallium-67 citrate scanning in sequence with Tc 99 m MDP could distinguish infection from other processes. Despite the initial promising results, sequential technetium–gallium scanning has demonstrated an accuracy rate of only 70 % [9]. Sequential gallium–technetium scanning is especially unreliable in patients having another lesion, such as non-union, surgery (Fig. 2), or a neuropathic joint at the site of the suspected osteomyelitis [9–11].

Indium-111-labeled leukocytes

Because of the difficulties encountered with interpretation of gallium-67 scans, many laboratories employ ^{111}In-labeled leukocytes in the evaluation of osteomyelitis. After intravenous injection, the labeled WBCs rapidly redistribute in the intravascular space with immediate images demonstrating activity in the lungs, liver, spleen, and blood pool. Images obtained at 24 h show activity only in the liver spleen and bone marrow. In a typical study, images of a particular region are acquired at 24 h following injection. Images at 4–6 h or even 30 min can be useful depending on the degree of inflammation. However, image quality generally improves significantly as blood pool activity decreases. An area of increased activity is a hallmark of a positive study. Cold lesions have been reported in 12 % [12] and are usually seen in areas rich with red marrow where a lesion appears relatively less active compared with adjacent high red marrow activity. When the site of infection is in the marrow-containing skeleton (spine, hips, knees) a bone marrow scan should be undertaken to further investigate an area of increased WBC accumulation. In such circumstances, if the bone marrow scan also reveals an

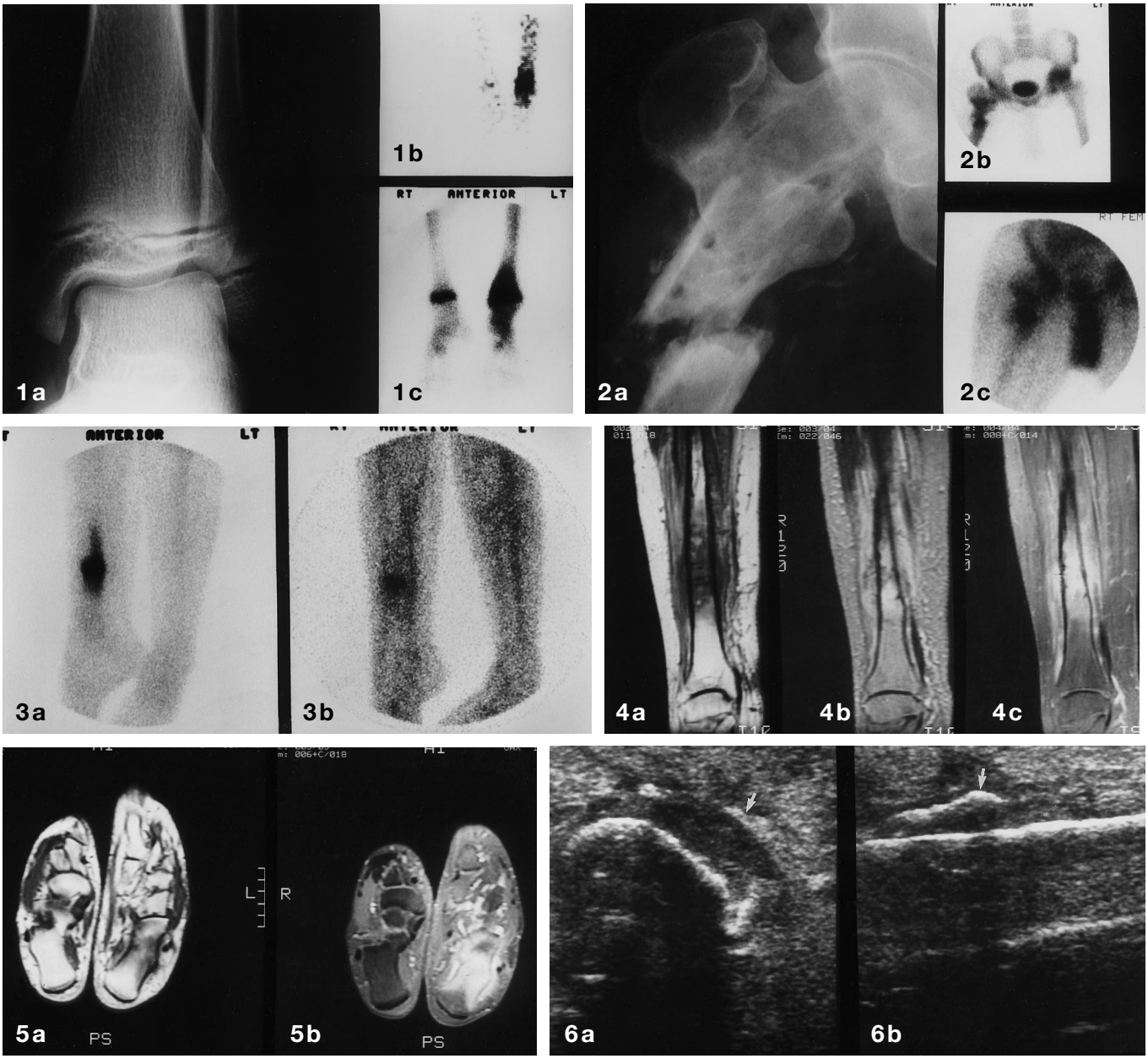

Fig. 1a–c. Plain film and Tc-99m-MDP in a 16-year-old patient with acute osteomyelitis of the left distal tibial metaphysis 10 days after the onset of symptoms. **a** Plain film shows no abnormality; **b** blood flow phase shows increased activity; **c** late phase shows increased bone tracer activity

Fig. 2a–c. Plain film, Tc-99m-MDP and gallium-67 citrate scans in a patient with fracture non-union 9 months following a car accident. No infection was found during re-exploration. **a** Plain films show sclerosis at fracture ends with no callus formation indicative of non-union; **b** Tc-99m-MDP late-phase bone scan shows increased activity at the fracture site; **c** Gallium-67 citrate (24 h) shows increased activity in the same area seen at bone scan

Fig. 3a, b. Tc-99m-MDP and Tc-99m-HMPAO white blood count scans in a patient with acute osteomyelitis of the distal shaft of the right tibia 1 month after the onset of symptoms. **a** Tc-99m-MDP late-phase bone scan shows increased bone tracer activity in the right tibia; **b** Tc-99m-HMPAO white blood count scan (2 h) shows increased tracer accumulation matching the area seen on bone scan

Fig. 4a–c. Magnetic resonance imaging study 2 days after scintigraphic studies of case in Fig. 3. **a** Coronal T1-weighted image shows abnormal low signal intensity due to marrow edema. **b** Coronal T2-weighted image shows abnormal high signal intensity in the marrow and in the soft tissues around the cortical bone due to edema. **c** Coronal T1-weighted fat-suppressed after contrast administration shows enhancement within the marrow and in the soft tissue around the cortex

Fig. 5a, b. Magnetic resonance imaging study in a diabetic patient with acute osteomyelitis of the left calcaneus 3 weeks after the onset of symptoms. **a** Axial T1-weighted image shows abnormal low signal intensity due to marrow edema in the left calcaneus. **b** Axial T1-weighted fat-suppressed after contrast administration shows enhancement within the calcaneal bone and in the soft tissue around it due to cellulitis

Fig. 6a, b. Ultrasound study in a patient with acute osteomyelitis of the right tibia 3 weeks after the onset of symptoms. Transverse and sagittal high-resolution real-time ultrasound scans showing periosteal elevation as a thick echogenic line *(arrow)* and anechoic subperiosteal pus accumulation in the antero-medial aspect of the tibial shaft

increased accumulation, this suggests increased hemopoiesis. A reduced accumulation on the bone marrow scan is compatible with osteomyelitis, but this can also occur in bone metastases, fractures, Paget's disease, surgical defects, and following irradiation [13]. In-WBC scanning appears generally superior to imaging with gallium-67. Merkel et al. [9] compared sequential technetium–gallium scan with ^{111}In-labeled leukocyte imaging in 42 patients with suspected low-grade sepsis. Overall, ^{111}In-labeled leukocyte scintigraphy was 83% sensitive and 94% specific. These results were by far superior to those of the sequential study with a sensitivity of 50% and specificity of 78%. In another study ^{111}In-labeled leukocyte study was only 60% sensitive for chronic osteomyelitis. The specificity was 96%. The decreased sensitivity of ^{111}In-Labeled leukocyte study in chronic osteomyelitis was thought to be due to a smaller number of granulocytes in chronic inflammation compared with the acute phase [8]. The demonstration of chronic foci of infection is better with ^{111}In-labeled leukocytes than with Tc-99m-labelled WBC (HMPAO). The concentration of Tc-99m WBC has been shown to be 30–40% lower than with In-WBC. There also appears to be a significant variation in cell labeling efficiency among different patches of HMPAO [14]. Long-term antibiotic therapy was not found to affect the diagnostic accuracy of the combined ^{111}In-WBC/Tc-99m-MDP scan result [15]. Although non-specific uptake generally appears to be less of a problem with ^{111}In-labeled leukocyte scans than with sequential technetium–gallium scans, numerous conditions, including fractures, arthritis, osteosarcoma, eosinophilic granuloma, pigmented villonodular synovitis, and neuropathic joints, have been reported to cause false-positive scans [11, 16]. During ^{111}In-labeled leukocyte scintigraphy the patient receives a significant dose of radiation which is of concern particularly in the pediatric age group. Despite these limitations, ^{111}In-labeled leukocyte scintigraphy is probably the study of choice for diagnosing and localizing osteomyelitis.

Indium-111-labeled polyclonal immunoglobulins

Recently, Nijhof et al. [17] investigated the efficacy of a non-specific polyclonal immunoglobulin (IgG) prepared from pooled human serum gamma globulin and labeled with ^{111}In via DTPA chelation (In-IgG). Experiments showed that infection due to specific bacteria were imaged with monoclonal IgG directed specifically against bacterial antigens [18]. During the first 24 h following injection, non-specific polyclonal IgG showed lesion uptake equal to that of specific monoclonal IgG, indicating an effective but non-specific mechanism of entrapment. After 24 h, specific monoclonal IgG showed greater lesion uptake than the control non-specific IgG. These results suggested the possible utility of polyclonal IgG for imaging infection and inflammation. Following intravenous injection, in addition to normal blood pool activity, prominent activity is seen in the liver and, to a lesser degree, in the spleen. The blood half-life is 24 h, and vascular activity is noticeable even at 48 h. There is no significant gastrointestinal activity, although urinary tract activity is seen. Clinical studies indicate that In-IgG is as efficacious as In-WBC or gallium-67 in the evaluation of focal infections. Oyen et al. [19] investigated In-IgG in 32 patients with positive bone scans. In 25 patients infection was suspected. In-IgG correctly identified the site of infections in all 25 patients. Early experience with In-IgG has shown many practical advantages over gallium-67 and In-WBC. Compared with gallium-67 there is no gastrointestinal or bone marrow activity that interferes with image interpretation. Compared with In-WBC, the simple preparation procedure eliminates the need for phlebotomy and laborious labeling method and reduces the patient radiation dose. There is apparently no significant bone marrow uptake. False-positive results are now being reported, however. These include Charcot joint, septic arthritis as well as non-infectious inflammatory pathology of the joints such as metabolic, reactive and auto-immune arthritis [17]. The main problems with labeled antibodies are slow blood clearance and relatively low lesion-to-background activity ratios.

Other scintigraphic agents

Technetium-99-m-labeled leukocytes

There continues to be much interest in developing leukocyte-based scintigraphy agents [20–22]; Tc-99m-labeled WBC offer several advantages over In-WBC including cost, availability, and dosimetry, leading to improved image quality and shorter acquisition time (Fig. 3). Tc-99m HMPAO is a lipophilic complex that has been shown to label leukocytes, predominantly granulocytes. The normal bio-distribution of Tc-99m HMPAO–WBC is similar to In-WBC. In a study of 100 patients with a variety of suspected infections and inflammation, a sensitivity of 100% and a specificity of 95% using Tc-99m HMPAO–WBC was reported [23]. In another study of 20 patients with suspected osteomyelitis, sensitivity was 100% and specificity was 93% [24]. Compared with In-WBC, bone marrow activity was more prominent, and this resulted in several false-positive findings. These studies indicate that Tc-99m–labeled WBC may be superior to In-WBC, particularly in low-grade osteomyelitis in which improved image resolution is mandatory. However, unwanted red marrow activity may continue to cause image misinterpretation.

Magnetic resonance imaging

Magnetic resonance imaging plays an important role in the diagnosis of musculoskeletal infections [25]. The excellent soft tissue bone marrow contrast resolution and multiplanar capability offer greater anatomical detail than CT or conventional radiograph. Marrow abnormality on MRI is a more sensitive indicator of disease than lytic changes seen radiographically and appears much

earlier in the course of the disease. Active osteomyelitis shows a low signal on T1-weighted images and appears as a high signal on T2-weighted images (Figs. 4, 5). This pattern represents a replacement of the marrow fat with water secondary to edema, exudate, hyperemia and ischemia. Short T1-weighted inversion recovery (STIR) and fat-selective saturation before and immediately after contrast enhancement are additional techniques used to improve the detection of osteomyelitis. As the disease becomes chronic, marrow signal becomes heterogeneous, and areas of high signal on T2-weighted images due to granulation tissue are seen. The MRI signal characteristics are non-specific, and a variety of bone diseases, such as tumors, neuropathic joints, and fractures, may increase water marrow content and can be indistinguishable from osteomyelitis. When the primary signs (low-signal T1-weighted and high-signal T2-weighted) of osteomyelitis on MR images are equivocal, secondary signs, including ulcer, cellulitis, soft tissue abscess, sinus tract, and cortical interruption, may help to augment diagnostic confidence and may also prove useful for the differentiation of osteomyelitis from processes that can mimic osteomyelitis, particularly neuropathic osteoarthropathy [26, 27]. Craig et al. [28] stated that the more intense the signal on T2-weighted or STIR and the presence of adjacent inflammatory soft tissue mass or ulcer, the greater our confidence will be to diagnose osteomyelitis and avoid the false-negative cases of non-infectious marrow edema. Several studies show impressive results with MRI in the evaluation of osteomyelitis, with reported overall sensitivities and specificities ranging from 92 to 100%, and 89 to 100%, respectively [5]. Morrison et al. [29] in a prospective study of 62 feet, 27 diabetic and 35 non-diabetic, evaluated the presence and extent of osteomyelitis. The MRI technique was also used to plan surgical resection and assess its cost-effectiveness as compared with bone scintigraphy. The sensitivity and specificity in diagnosing osteomyelitis were 82 and 80%, respectively, in diabetics, and 89 and 94%, respectively, in non-diabetics. There was no evidence of recurrent infection at the surgical margin in 13 feet in which the area of limited resection had been delineated at MR imaging, thus making this imaging modality clinically useful and cost-effective compared with scintigraphy. The MRI technique appears promising in the diagnostic work-up of osteomyelitis but remains of limited use for whole-body examination. This is important particularly in the pediatric age group where multifocal disease is seen in 7% [30]. Artifacts from metallic implants and prostheses decrease the yield of MRI and may even make it non-diagnostic. The MRI technique cannot be performed on patients who are unstable hemodynamically or unable to be confined.

Computed tomography

Computed tomography may have a role in the diagnosis of osteomyelitis. It is superior to MRI for visualizing bony destruction, gas in the bone [31], and a bony sequestration [32]. It can demonstrate abnormalities earlier than conventional radiographs and is useful in the spine, pelvis and sternum [5, 33]. Spiral CT with multiplanar reconstruction is superior to standard CT and is particularly important in the diagnosis of sternoclavicular osteomyelitis and its complications [34]. Early findings of osteomyelitis may include intramedullary gas or increased marrow density; the latter may be difficult to appreciate because of the higher attenuation from surrounding cortical bone. Chronic osteomyelitis shows sclerosis, demineralization, periosteal reaction, and often sequestra; in these circumstances, CT may be significantly better than plain films since the problem of overlapping bone may be resolved.

Ultrasonography

Ultrasound may be utilized as a relatively simple and inexpensive technique following clinical examination, conventional radiographs, and bone scintigraphy, because it is quick and lacks ionizing radiation, which is an advantage particularly in children [35]. It may provide information that determines the need for other more costly investigations such as scintigraphy, CT, and MRI. The examination needs a set of linear transducers of high frequency in the 5-, 5.7-, and 10-MHz range for the evaluation of relatively superficial structures.

In acute osteomyelitis the US changes are demonstrable just 1 or 2 days after the onset of symptoms [36]. The US appearances of osteomyelitis include soft tissue abnormalities and periosteal elevation that manifest as a single or multiple echoic lines surrounding the cortical bone (Fig. 6). Ultrasound can also demonstrate some irregularity and interruption of the cortical bone. Subperiosteal fluid is an anechoic or hypoechoic collection separating the periosteum from the cortical bone [37]. Hematoma or tumor developing under the periosteum may have a similar US appearance; therefore, clinical correlation is mandatory. Ultrasound-guided needle aspiration can be useful in obtaining material for bacterial culture [38]. Subperiosteal abscess drainage percutaneously with the help of US and fluoroscopy may be an alternative to surgical drainage when medical therapy alone is inadequate [39].

Even with its advantages, US in musculoskeletal sepsis has not achieved broad acceptance by radiologists. The most important reasons may in part explain the limited level of interest in this modality. The first reason is due to the technical limitations due to a small field of view permitting exploration of only a narrow segment of an anatomical area at a time. The second reason is that it must compete with the high-quality images produced by MR imaging [40]; however, despite these limitations, interest in US continues to develop.

Osteomyelitis in children

Infection in the pediatric age group almost always occurs by hematogenous colonization of growing bones by bacteria, usually *Staphylococcus aureus* [41]. The

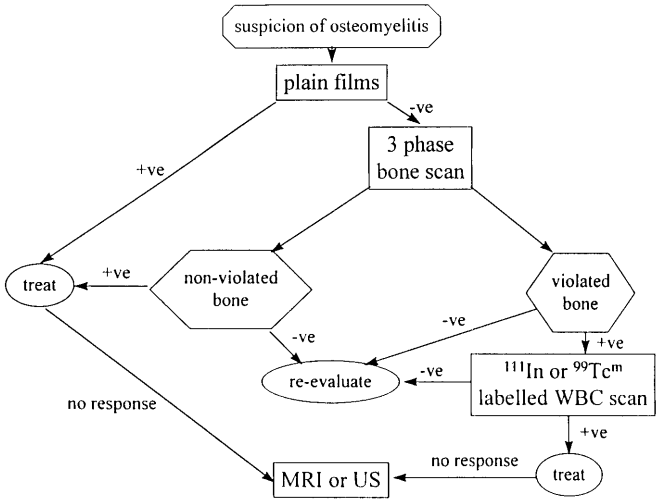

Fig. 7. Algorithm showing imaging suggestions for evaluating osteomyelitis. This algorithm can be used in general in many instances. Obviously there are many alternatives possible. Also in specific situations a different algorithm may be preferable. In specific situations indium-111 or labeled white blood count scan can be replaced by MR imaging. Also when studies are contradictory or equivocal MR imaging may be used to solve this problem

metaphysis is usually the site of infection. In children this is difficult to evaluate by scintigraphy and MRI. The high blood flow and significant rate of bone deposition result in increased uptake of radio-pharmaceuticals, and osteomyelitis producing increased tracer uptake adjacent to the physis may pass undetected [30]. Similarly, metaphyseal disease can be obscured on T1-weighted MR images by the adjacent water-rich marrow. T2-weighted images and STIR sequence show less signal intensity in normal hematopoietic marrow than in marrow infiltrated by infectious exudate.

Conventional films should be obtained initially in every patient with suspected osteomyelitis. Radiographs may detect soft tissue edema as early as 48 h after the onset of symptoms, but are insensitive if bone destruction is less than 30% [41]. Plain films may be useful in excluding other causes that can appear similar to osteomyelitis on scintigraphy and MR images.

Reports in the literature suggest that adequately performed skeletal scintigraphy and MRI are both highly sensitive and specific in detecting uncomplicated acute hematogenous osteomyelitis in children. Scintigraphy is preferred to MRI for the initial evaluation, it is less expensive, rarely requires sedation [42], and children can be scanned more than once, thus improving detection rate. The capability of imaging the entire skeleton is particularly important in infants and neonates in whom the localizing signs are poor [43]. The MRI technique is reserved for cases that require surgical intervention, such as infections of the spine, pelvis, and infections that extend into the physis and fail to respond to antibiotic treatment [30].

In view of the success of investigating children with conventional radiographs, scintigraphy, and MRI, what is the role of US in current clinical practice? There are some immediate and obvious advantages to employing US to evaluate osteomyelitis: It is a non-invasive, easily available technique which does not use ionizing radiation, and in subperiosteal abscess US-guided aspiration and drainage may prove useful in some cases.

Conclusion

It is clear from this review that no single imaging modality is ideal for the diagnosis of osteomyelitis. The decision for the most suitable imaging modality can sometimes be difficult, but with the combined effort of both the physician and radiologist this goal can be achieved with confidence. Finally, in an attempt to simplify and summarize our approach to the diagnosis of osteomyelitis, we suggest the algorithm in Fig. 7.

Acknowledgements. We are grateful to Prof. Bloem for his tremendous effort in reviewing and correcting the manuscript, and to Mrs. S. Ferguson and Mrs. E. Henderson for typing this manuscript.

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