Imaging in Osteomyelitis and Septic Arthritis

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Opinion statement

The diagnosis of osteomyelitis and septic arthritis depends on clinical presentation, appropriate cultures, laboratory tests, and imaging studies. During the initial evaluation of a patient suspected of having these musculoskeletal infections, radiography, ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT), and radionuclide scans selectively are ordered to assist in the diagnosis, assess the extent of involvement, and guide the site selection for the bone biopsy. Conventional radiography should be performed on all patients. Radiographic changes in early osteomyelitis often are difficult to interpret and lag at least 2 weeks behind the evolution of infection. In patients with septic arthritis, radiographic images often are not revealing in the first few days of infection. However, initial radiographic images may be used to determine associated conditions such as osteoarthritis or simultaneous osteomyelitis, or to exclude neoplasm or injury. Therefore, after the infectious or inflammatory process has been detected and localized with this technique, further examinations by CT, MRI, biopsy, and cultures may be necessary to delineate the extent and etiology of the process. The use of ultrasound in the diagnosis of osteomyelitis is limited to the detection of soft tissue abnormalities around the bone. Ultrasound is a very powerful tool to detect early fluid effusions and to guide initial joint aspiration and drainage procedures. Ultrasound is the method of choice for treatment of patients with acute septic arthritis. CT provides images that display high spatial resolution and explicit cortical bony detail in patients with osteomyelitis. However, CT scans have limited use during the early stages of septic arthritis. MRI is superior to CT in localizing marrow extension and soft tissue changes. In patients with vertebral osteomyelitis, MRI should be used. MRI has the highest accuracy of all imaging techniques. The spatial resolution of MRI makes it more useful than CT or scintigraphy in the diagnosis of septic arthritis. Imaging with radiopharmaceuticals provides information regarding the pathophysiologic and pathobiochemical processes of inflammation, whereas radiography provides high-resolution morphologic information about the pathologic process. Technetium-99m methylene diphosphonate (^{99m}Tc MDP) usually is positive in biopsy-confirmed cases of hematogenous osteomyelitis. However, conditions that result in bone injury and repair cause constant bone turnover and focal uptake of ^{99m}Tc in bone. Using a three-phase ^{99m}Tc MDP followed by gallium-67 imaging increases specificity. Indium-111–labeled white blood cell (In-111 WBC) scintigraphy is very sensitive (except in some cases of chronic osteomyelitis), specific, and the method of choice for diagnosing and localizing distal appendicular skeletal osteomyelitis.

Introduction

OSTEOMYELITIS

Osteomyelitis is defined as infection of the bone [1••]. Normal bone is highly resistant to infection, which occurs only as a result of a large organism inoculation, trauma that results in bone damage, or the presence of foreign bodies. When the bone is colonized and an active acute infection occurs, the infection may resolve, may become a quiescent, persistent infection, or may become a chronic infection with associated progressive bone deterioration [2]. The pathogenesis of osteomyelitis has been explored clinically, and different types of osteomyelitis can be classified according to the source of the infection (*ie*, hematogenous or contiguous focus) and the vascular capability of the host (*ie*, with or without generalized vascular insufficiency) [3–5].

Hematogenous osteomyelitis The metaphysis of the long bones (tibia, femur) are involved most frequently. In infants, medullary infection may spread to the epiphysis and joint surfaces through capillaries that cross the growth plate [6]. In the child older than 1 year, the growth plate is avascular and the infection is confined to the metaphysis and diaphysis. The joint is spared unless the metaphysis is intracapsular. Thus, cortical perforation at the proximal radius, humerus, or femur enables the infection to migrate to the elbow, shoulder, or hip joint, regardless of the patient's age. A pathogenic species is almost always recovered from infected bone [3–5]. *Staphylococcus aureus* is the most common organism isolated in infants, children, and adults [7].

Hematogenous osteomyelitis can be found in the adult population. In long bones, the infection usually begins in the diaphysis but may spread to involve the entire medullary canal. Extension into the epiphysis and joint space may occur because the growth plate has disappeared and the medullary areas are contiguous. Because the periosteum is firmly adherent to the bone, cortical penetration usually leads to a soft tissue abscess. Subperiosteal abscesses and massive cortical devitalization rarely occur. Sinus tracts connecting the sequestered nidus of infection to the skin through soft tissue extension may form. The involucrum contains the sequestered, necrotic marrow and endosteal bone. Sequestra often are found within the thickened cortex and are surrounded by reactive bone and chronic granulations. Brodie's abscess is the name given to a chronic localized bone abscess. Patients with subacute cases may have fever, pain, and periosteal elevation, whereas chronic cases are often afebrile with long-standing dull pain. The most common site of involvement is the distal part of the tibia, and the lesion typically is single and located near the metaphysis.

Vertebral osteomyelitis Vertebral osteomyelitis in the adult population usually is hematogenous in origin but may be secondary to trauma. An early involvement of the anterior-inferior edge of the vertebral body suggests spread from the bony entrance of the anterior spinal artery [8,9]. Retrograde infection through Batson's venous plexus is also postulated [10]. The segmental arteries that supply the vertebrae usually bifurcate to supply two adjacent bony segments. Therefore, the disease often involves two adjacent vertebrae and the intervertebral disk.

The lumbar region is affected in at least 50% of patients with hematogenous vertebral osteomyelitis. The thoracic spine is affected in at least 35% of patients and the cervical spine in at least 20% of patients [11]. However, in intravenous drug abusers, the cervical vertebrae are involved much more often (27%), and the thoracic vertebrae much less frequently (4.5%).

The infection may extend into the cartilaginous endplate, disk, and/or adjacent areas. Posterior extension of the infection may cause epidural and subdural abscesses, or even meningitis. Extension anteriorly or laterally may cause paravertebral, retropharyngeal, mediastinal, subphrenic, or retroperitoneal abscesses. Spread to adjacent vertebral bodies may occur rapidly through the rich venous networks in the spine.

The infection usually is monomicrobic when hematogenous in origin [12]. In the normal host, *S. aureus* remains the most commonly isolated organism. However, aerobic gram-negative rods, including *Pseudomonas aeruginosa* and *Serratia marcescens*, are found often in intravenous drug users and patients with urinary tract infections [12,13]. Positive culture results are important for diagnosis because conditions such as trauma and vertebral collapse may simulate infection.

Contiguous focus osteomyelitis without generalized vascular insufficiency In the past, osteomyelitis resulting from acute penetrating trauma has been referred to as contiguous focus osteomyelitis [3]. Although the term contiguous focus insinuates that the infection is caused by an adjacent soft tissue infection, chronic contiguous focus osteomyelitis also can begin as an acute infection, with the organisms being inoculated directly into the bone at the time of trauma. The organisms also can be spread by nosocomial contamination during preoperative or intraoperative procedures.

Multiple pathogenic species usually are isolated from the infected bone in these cases. *S. aureus* and coagulase-negative staphylococci account for 75% of the isolated bacterial species [14]. However, gram-negative bacilli and anaerobic organisms are isolated frequently. In chronic osteomyelitis, there are usually

large areas of devitalized cortical and cancellous bone within the wound.

Contiguous focus osteomyelitis with generalized vascular insufficiency General vascular insufficiency makes appropriate therapy and management of contiguous osteomyelitis difficult. Most of the patients in this category have diabetes mellitus [15]. The small bones of the feet, talus, calcaneus, distal fibula, and tibia commonly are involved in this category of infection. Multiple organisms are found in patients with diabetic foot osteomyelitis including *S. aureus*, coagulase-negative *Staphylococcus* species, *Streptococcus* species, *Enterococcus* species, gram-negative bacilli, and anaerobes [15]. Osteomyelitis in vascular-compromised patients can be difficult to diagnose; thus, imaging can play an important role. Malignant external otitis (necrotizing external otitis) is an unusual but potentially fatal infection that may occur in elderly diabetic patients. Most of these infections are mediated through *Pseudomonas* species.

SEPTIC ARTHRITIS

Septic arthritis is an inflammation of the joint space, synovial fluid, synovium, and articular cartilage caused by a variety of microorganisms [16••]. Most septic joints develop as a result of hematogenous seeding of the vascular synovial membrane. The synovial membrane has no limiting basement plate, which allows easy entry of bacterial organisms. Septic arthritis occasionally can result from joint aspiration or joint injection. Bacterial arthritis has been reported secondary to penetrating trauma or after direct trauma to a joint without an obvious break in the skin. When a bone infection breaks through the outer cortex and into the intracapsular region, a joint infection can result.

Almost every bacterial organism has been reported to cause septic arthritis. However, acute infections generally are caused by pyogenic bacteria and called acute bacterial or septic arthritis. The process generally is acute and constitutes a medical emergency. If untreated for even 24 to 48 hours, permanent joint damage may result. A permanent loss in joint function is seen in approximately 40% of patients with nongonococcal septic arthritis but ranges from 10% to 73% [17–20]. The mortality associated with this disease usually ranges from 5% to 20% and is often a result of the transient or chronic bacteremia that causes most of the cases of septic arthritis [17–21]. Therefore, prompt recognition, rapid and aggressive antimicrobial therapy, and surgical treatment are critical to ensuring a good prognosis. Even with prompt diagnosis and treatment, high mortality and morbidity rates still occur. Common pyogenic bacteria, including *S. aureus*, *Streptococcus* species, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*, cause most of the episodes. The aerobic gram-negative bacilli and anaerobes account for additional cases.

In contrast, gonococcal arthritis often is treated successfully with antimicrobial therapy and demonstrates a very low rate of complications and an excellent prognosis for full return of normal joint function. In patients with prosthetic joint infections, the hardware must be removed eventually by a two-stage revision to cure the infection. Chronic infections most often are caused by mycobacteria or fungi and follow a chronic indolent course. Sterile or reactive arthritis is an inflammatory reaction that generally is secondary to infection in another part of the body. It may be associated with infection preceding hepatitis or postgastrointestinal infections with *Salmonella* species or *Shigella* species.

Although diagnosis depends on the isolation of the bacterial species from synovial fluid samples, patient history, clinical presentation, laboratory findings, and imaging studies are also important. Imaging studies of septic arthritis can be used only to support or dissuade a clinical suspicion of the disease and should not be used as an absolute diagnostic indicator.

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Jon T. Mader, MD, passed away on October 25, 2002.

Treatment

Procedures

Conventional radiography

Standard procedure Radiographic changes in patients with early osteomyelitis are often difficult to interpret and lag at least 2 weeks behind the evolution of infection because a 30% to 50% loss of bone density must occur before a radiograph shows abnormality [22]. This also means that when the patient is undergoing appropriate antimicrobial therapy, radiographic improvement may lag behind clinical recovery. The earliest radiographic changes are soft tissue swelling, periosteal thickening or elevation (or both), and focal osteopenia. These findings are subtle and may be missed. Edema, abscess formation, and trabecular destruction also may be detected. The more diagnostic lytic changes are delayed and often associated with an indolent infection of several months' duration. Trabecular resorption can be viewed as mottled areas of radiolucency in patients with chronic osteomyelitis.

Infants and children are capable of generating a significant periosteal response to the infection, which results in substantial formation of bone at the margin of the infection, which is called an involucrum. Joint effusion adjacent to the area of bone infection is often present. Also, subperiosteal abscess and extensive periostitis (inflammation of the periosteum) can be seen in this patient population. The necrotic endosteal bone fragments and marrow (sequestra) often are found within the thickened cortex and are surrounded by reactive bone and chronic granulations. Involucrum, a layer of living bone surrounding the sequestra, also may be found. In the long bones of adults, the infection usually begins in the diaphysis but may spread to involve the entire medullary canal. Extension into the epiphysis and joint space may occur because the growth plate has disappeared and the medullary areas are contiguous. Because the periosteum is firmly adherent to the bone in the mature skeleton, cortical penetration usually leads to a soft tissue abscess, whereas subperiosteal abscesses and massive cortical devitalization rarely occur. Sinus tracts connecting the sequestered nidus of infection to the skin through soft tissue extension (cloacae) may form. Whereas the sensitivity of conventional radiography to detect osteomyelitis of the diabetic foot is low, the specificity approaches those of radionuclide bone scans (discussed later). Degenerative or inflammatory arthritis and neuropathic joints generate false-positive results with conventional radiography.

In cases of septic arthritis, radiographic images often are not revealing in the first few days of acute infection because they usually are normal or show only preexisting joint disease. However, swelling of capsule and soft tissue around the affected joint, fat pad displacement, and in some patients, joint space widening caused by localized edema and effusion may be seen. The initial radiographic image may be used to determine associated conditions such as osteoarthritis or simultaneous osteomyelitis, or it may be used as a baseline image to monitor response to treatment. These conventional images often can exclude neoplasm or injury. As the infection progresses, radiographic detection of diffuse joint space narrowing caused by cartilage destruction is possible. Radiographs can evaluate late, inadequately treated stages of septic arthritis in which generalized joint destruction, osteomyelitis, osteoarthritis, joint fusion, calcifications in the periarticular tissues, or subchondral bone loss followed by reactive sclerosis are seen.

Contraindications The risk of patient or fetal exposure to ionizing radiation is debated.

Special points Because of the degree of the sclerosis and nonspecific radiographic changes in some patients with osteomyelitis, it often is difficult to gauge the extent of infection by visualizing the radiograph. Gauging the extent of infection may require careful clinical (and ultimately surgical) evaluation. It often is difficult to distinguish an infected nonunion from one that is uninfected. Therefore, after the infectious or inflammatory process has been detected and localized with this technique, other imaging modalities may be necessary to delineate the extent and etiology of the process.

Although conventional radiography often lacks sensitivity, it should be the initial imaging technique for patients with musculoskeletal infection.

Cost effectiveness This imaging technique is the least expensive and most readily available.

Ultrasound

Ultrasound is a noninvasive, inexpensive, and easy-to-use imaging technique that is devoid of irradiation or any other known complications. It also allows for real-time imaging, which enables guided aspiration of fluid collections for obtaining clinical samples or accomplishing drainage [23••].

Standard procedure The use of ultrasound in the diagnosis of osteomyelitis is limited to the detection of soft tissue abnormalities around the bone because the ultrasound beam cannot cross the cortical bone and document bone marrow discontinuities. Detection of abscess or fluid collections next to the cortex is highly suspicious of osteomyelitis. Ultrasound may be used to evaluate the vascularity of soft tissues in patients with suspected diabetic foot osteomyelitis through the use of color and power Doppler. Ultrasound has great efficacy in evaluating the state of the soft tissues and the presence of fluid accumulations next to prosthetic implants, without being impaired by metal artifacts.

Although ultrasound has limited use in osteomyelitis diagnosis, it is capable of showing intra- and extra-articular abnormalities not apparent by plain radiography, which are indicative of inflammation and possibly septic arthritis. Ultrasound is a very powerful tool to detect early fluid effusions and to guide initial joint aspiration and drainage procedures. Even small collections of fluid (1 to 2 mL) can be detected accurately. Non–echo-free effusions (caused by clotted hemorrhagic collections) are characteristic of a septic joint. It has been suggested that the presence of an echo-free effusion (caused by transient synovitis and fresh hemorrhagic effusions) may rule out the diagnosis of septic arthritis. This imaging technique is useful for detecting collections of fluids in deep joints, including the hip. The status of the intra-articular compartment, joint capsule, bony surface, adjacent soft tissues, and the patient's response to therapy can be monitored.

Special points Use care during ultrasound procedures to prevent applying excessive pressure with the transducer and avoid collapsing fluid accumulations within the joint and missing the diagnosis.

The use of spatial compound sonography (a method that obtains sonographic information from several different angles of insonation and combines them to produce a single image) can improve the image quality of musculoskeletal images by reducing speckle and improving definition of tissue planes [24].

Cost effectiveness Inexpensive if ultrasound-trained personnel and instrumentation are available.

Computed tomography

It usually is not necessary to obtain computed tomography (CT) images in cases of osteomyelitis. However, in certain circumstances, such as a patient with chronic osteomyelitis or early acute hematogenous osteomyelitis, diagnosis may be aided with CT scans to help gauge the extent of bone and soft tissue infection.

Standard procedure CT provides images that display high spatial resolution and explicit cortical bony detail from patients with osteomyelitis [25••]. This imaging method is very useful in guiding bone biopsy and detecting very small sequestra, cortical abnormalities, soft tissue extension, hyperattenuation and constriction of the medullary cavity, destruction of cortical bone, and new bone formation. Differentiation between cranial osteomyelitis and soft tissue infection and monitoring the response to therapy for patients with malignant external otitis is done best with serial CT. CT accurately can display anatomic detail to view end-plate erosions and paravertebral masses in patients with vertebral osteomyelitis. After the injection of an intravenous contrast medium, an inflammatory hyperemia may be seen as enhancement of the intervertebral disk.

Spiral CT scans that use narrow collimation (4 mm) and close interscan reconstruction (2 to 4 mm) after the injection of a radiopaque dye emerged in the 1990s. These scans have less inter- and intrascan time and provide higher-quality images with superior detail than regular CT scans. Volumetric data collection enables three-dimensional reconstruction without the artifacts found in other scanning procedures, thereby yielding additional spatial information of abscess and fluid collections to guide surgical procedures accurately.

Similar to radiographs, CT scans have limited use during the early stages of septic arthritis. However, these scans may enable the visualization of joint effusion, soft tissue swelling, and periarticular abscesses. CT is more sensitive than plain radiographs in the imaging of joint space widening caused by localized edema, bone erosions, foci of osteitis, scleroses, and adjoining osteomyelitis. This scanning technique may be useful in the diagnoses of patients with arthritis who are difficult to assess, including those with infections of the hip, sacroiliac, and sternoclavicular joints. CT scans may assist in guiding joint aspiration, selecting the surgical approach, and monitoring therapy in patients with these difficult infections [26].

Contraindications The risk of patient or fetal exposure to ionizing radiation is debated.

Special points Differentiation of sequestra from osteoid osteomas may be problematic. However, sequestra usually are shaped irregularly and the calcified nidus is located in an eccentric location. Noninfectious hemorrhage, neoplasm, stress fracture, and/or radiation therapy have similar CT-detected increases in intramedullary density as infectious inflammation does.

One disadvantage of this study is the scatter phenomenon, which occurs when metal is present in or near the area of bone infection. This scatter effect causes a significant loss of image resolution.

Cost effectiveness The costs associated with this diagnostic technique often make its widespread use cost-prohibitive.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) has become a useful diagnostic procedure for the early determination and extent of musculoskeletal infection [27,28]. MRI displays greater resolution for soft tissue abnormalities than CT scans or radiographs and greater anatomical detail than radionuclide scans. As with CT imaging, it is usually not necessary to accomplish imaging studies with MRI in many patients with osteomyelitis. However, it is the method of choice for the diagnosis of vertebral osteomyelitis and may be used on an individual basis in complicated patients with early acute and chronic osteomyelitis, particularly those with deep pelvic infections. MRI is a useful scanning technique in cases of septic arthritis.

Standard procedure MRI is a useful modality for differentiating between bone and soft tissue infection [25••]. Initial MRI screening for patients with osteomyelitis usually consists of T1- and T2-weighted spin echo pulse sequences. The sensitivity of MRI may be increased with short-tau inversion recovery (STIR) because these images produce high signal intensity for tissue with long T1 or T2. Although STIR images are highly selective for abnormalities with a negative predictive value for acute osteomyelitis nearly 100%, they have a lower specificity and a lower spatial resolution than conventional T1 and T2 images. Gadolinium diethylenetriaminepentaacetic acid (Gd-DPTA)-enhanced T1-weighted imaging provides additional information because enhanced images represent viable tissues with intact or increased vascularity. Rim enhancement is indicative of inflammation surrounding a necrotic core of tissue. A lack of image enhancement often can rule out infection.

The typical appearance of osteomyelitis is a localized area of abnormal marrow with decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. There may be decreased signal intensity on T2-weighted images. Post-traumatic and surgical scarring of the bone marrow show a region of decreased signal intensity on T1-weighted images with no change on the T2-weighted image. This imaging modality is superior to CT in localizing marrow extension and soft tissue changes. The sensitivity and specificity of MRI to detect patients with osteomyelitis range from 68% to 100% and 50% to 100%, respectively [25••,29].

This imaging modality is extremely useful in patients with vertebral osteomyelitis and has a sensitivity of 96% and specificity of 92% [30]. Decreased disk space height is obvious on all pulse sequences. MRI can be used with high sensitivity and specificity in children with acute hematogenous osteomyelitis. The ability of MRI to reveal abscesses, subperiosteal fluid collections, sequestra, and sinus tracts in chronic osteomyelitis is well-documented. Brodie's abscess appears with low intensity on T1-weighted images, high intensity on T2-weighted images, and rim enhancement in Gd-DPTA–enhanced T1-weighted imaging. The transition zone between affected and healthy marrow is well-defined when compared to the wide transition zone seen in patients with acute osteomyelitis. The hallmark of chronic osteomyelitis (the sequestrum) shows low signal intensity on all pulse sequences, whereas sinus tracts are seen as areas of high signal intensity on the T2-weighted image extending from the marrow and bone through the soft tissues and skin. MRI has the highest accuracy in patients with diabetic foot osteomyelitis, with a sensitivity of 82% and specificity of 80% [31]. However, detection is improved through the use of STIR and Gd-DPTA–enhanced T1-weighted imaging. Discrimination between osteomyelitis and the pathologic features of joint neuropathy of the dia-

betic foot may be accomplished by noting that neuropathic joints have low signal intensity on all pulse echo sequences, whereas high marrow signal intensity exists in T2-weighted images in osteomyelitis.

The spatial resolution of MRI makes it more useful than CT or scintigraphy in the diagnosis of septic arthritis because MRI can visualize even minuscule joint effusions and can better differentiate between bone and soft tissue infections. Furthermore, patients do not have to be exposed to ionizing radiation. Initial MRI screening of septic arthritis usually consists of T1- and T2-weighted spin echo pulse sequences. In a T1-weighted study, edema and fluid are dark, whereas fat is bright. In a T2-weighted study, the opposite is true. Therefore, joint effusions, abscesses, and soft tissue edema will generate a high signal on T2-weighted images. MRI may be useful particularly in aiding the diagnosis of joint infections that are difficult to access, such as sacroiliitis [32]. As with osteomyelitis, Gd-DPTA–enhanced MRI may increase detection sensitivities.

Special points The main disadvantages of MRI are high cost, lack of universal availability, imaging interference caused by metal implants, and lower resolution of calcified bone structures and the cortex [33].

Many other conditions, including trauma, infarct, ischemia, or neoplastic process, may resemble osteomyelitis in MRI. Specifically, osseous tissue metabolic conditions, fracture healing, metastasis, osteonecrosis, and bone contusions may demonstrate similar T2-weighted images as those seen in cases of osteomyelitis. In the diabetic foot, MRI may not be able to distinguish between a rapidly progressive neuropathy and osteomyelitis. As with the other imaging techniques, MRI is nonspecific and is unable to differentiate between infectious and noninfectious inflammatory arthropathies [34]. Because the differentiation of infection from neoplasm on the basis of the MRI may be difficult, clinical and radiographic correlation is mandatory.

In children younger than 6 years, MRI often requires patient sedation.

Cost effectiveness The cost and availability make this imaging technique prohibitive. However, MRI should be performed in patients with suspected vertebral osteomyelitis.

Radionuclide scans

Over the past few decades, radiopharmaceuticals have proven useful in the diagnosis of patients with suspected osteomyelitis and septic arthritis [35••]. Imaging with radiopharmaceuticals provides information regarding the pathophysiologic and pathobiochemical processes of inflammation, whereas radiography provides high-resolution morphologic information about the pathologic process. A procedure should have high sensitivity and be applicable for whole body use for the detection and localization of osteomyelitis. Nuclear medicine imaging procedures typically have these characteristics. Radionuclide scanning may be used in cases of chronic osteomyelitis, early acute hematogenous osteomyelitis, suspected orthopaedic implant infection, or bone infections of the diabetic foot in which diagnosis may be problematic [36].

Standard procedure The usefulness of the technetium-99m methylene diphosphonate (^{99m}Tc MDP) scintigraphy imaging technique in the initial evaluation of osteomyelitis has remained significantly high despite its lack of specificity. These scans demonstrate increased isotope accumulation in areas of increased blood flow and reactive new bone formation. It usually is positive in biopsy-confirmed cases of hematogenous osteomyelitis as soon as 48 hours after the initiation of the infection. Sensitivity and specificity of osteomyelitis detection range from 69% to 100% and 38% to 94%, respectively. The specificity of ^{99m}Tc MDP bone scintigraphy in detecting osteomyelitis is improved with the use of three-phase studies (the arterial phase, the blood-pool and tissue perfusion phase, and the static bone phase), especially in differentiating bone from soft tissue infection [37]. The three-phase bone scan has limitations. Because ^{99m}Tc phosphate compounds accumulate at the site of bone repair, conditions that can result in bone injury and repair such as trauma, surgery, or implanted orthopaedic hardware cause constant bone turnover and focal uptake of ^{99m}Tc, which suggests osteomyelitis. The use of ^{99m}Tc MDP eliminates some of the problems associated with other radiopharmaceuticals (*eg*, the dependence on in vitro manipulation of autologous blood for indium-111–labeled white blood cells [In-111 WBC], discussed later). In

addition, ^{99m}Tc compounds have a substantially reduced radiation dose, gamma radiation levels suitable for recording devices, high availability, low cost, and excellent imaging characteristics [38,39]. The short half-life of ^{99m}Tc means that reimaging can be performed at intervals of 2 days.

Three-phase scintigraphy usually must be followed by gallium-67 (Ga-67) citrate imaging for confirmation of osteomyelitis. The addition of Ga-67 scintigraphy is helpful in defining the presence and intensity of the inflammation. However, uncertainty remains as to whether the increased localization of ^{99m}Tc MDP or Ga-67 in some patients results from excessive new bone formation or sepsis [40]. Ga-67 scans do not have very good imaging characteristics and have the disadvantage of a 24- to 48-hour delay for localization [41,42].

The use of other techniques, such as indium-111 chloride (^{111}InCl) [43], has replaced Ga-67 citrate for imaging of deep-seated infections [38,39,44]. Similar to Ga-67, ^{111}InCl attaches to serum proteins and leaks from the blood stream into areas of inflammation. In contrast to Ga-67, ^{111}InCl is more heavily concentrated by hematopoietic tissue and is not found to accumulate in areas of reactive bone.

Another scanning modality that uses In-111 WBC scintigraphy isolates a sample of the patient's leukocytes, labels it with In-111, and injects it back into the patient. These radiolabeled leukocytes localize into areas of acute infection according to host inflammatory cytokine and chemokine gradients. It is very accurate, specific (except in some patients with chronic osteomyelitis), and the radionuclide method of choice for diagnosing and localizing appendicular skeletal osteomyelitis [45]. The usefulness of this imaging procedure is well-documented when combined with bone marrow imaging with ^{99m}Tc sulfur colloid marrow scintigraphy in patients with suspected orthopaedic implant infection, because leukocyte uptake around prostheses may be secondary to surgery. Accumulation of leukocytes combined with noncongruent bone marrow patterns and absent marrow uptake is highly indicative of infections. This imaging technique also demonstrates significant efficacy in patients with suspected diabetic foot infection, especially when combined with ^{99m}Tc MDP scanning to provide anatomic landmarks to distinguish between cellulitis and osteomyelitis. In-111 WBC in combination with marrow scintigraphy is effective in diagnosing osteomyelitis in the neuropathic joint of a patient with a diabetic foot.

Indium-111–labeled white blood cell scans are not as beneficial in patients with chronic osteomyelitis, and false-negative results often occur in this patient subset. Other problems with In-111 WBC scintigraphy are the 24-hour delay required for imaging, high levels of radiation in the spleen, and limited injection dose. Therefore, ^{99m}Tc hexamethylpropyleneamineoxime leukocytes were developed to remedy these problems with In-111 WBC imaging. Images are administered usually 3 to 4 hours after injection, and the patient receives a significantly lower radioactive dose. Therefore, this technique is recommended for children and those patients with acute or exacerbated chronic infections. However, urinary and fecal excretion of the ^{99m}Tc compound may mask abdominal structures and lower sensitivity in chronic infections because of an inability to collect delayed images. This scanning technique, if negative, is sufficient for ruling out infection if clinical suspicion of osteomyelitis exists for a diabetic foot and is the method of choice in the early postoperative phase.

Radionuclide scans are of limited use in patients with septic arthritis. However, Ga-67 and ^{111}InCl scans often can detect localized areas of inflammation by attaching to serum proteins that leak from the blood stream into areas of inflammation. They also show increased isotope uptake in areas of concentrated polymorphonuclear leukocytes, macrophages, and malignant tumors. Although these scans are somewhat sensitive, they do not show joint detail well, and it often is difficult to distinguish between bone, joint, and soft tissue inflammation. In-111 WBC also may play a role in diagnostic imaging of acute septic arthritis. Although this scan is positive in approximately 60% of patients with septic arthritis, false-positive results may occur in patients with synovitis secondary to active osteoarthritis [46]. These scintigraphic methods cannot differentiate from patients with inflammatory arthritis and usually are used only to rule out concomitant osteomyelitis.

Complications There are documented cases in which the in vitro manipulation and reinjection of patients' labeled blood resulted in infection or cross-contamination between patients. There is a biohazard risk to technicians with this imaging modality.

The risk of patient or fetal exposure to radiation is debated.

Special points Three-phase ^{99m}Tc MDP scans are very sensitive in the detection of osteomyelitis, with a sensitivity of 92% and specificity of 94% in nonviolated bone [47]. However, false-positive rates have been reported from 0% to 64% in reported series [48] and high rates can be attributed to cases of new bone formation, fracture healing, heterotopic ossification, arthritis, and local minor trauma [38]. High false-positive rates also have occurred in patients with soft tissue infections such as the diabetic foot, decubitus ulcer infections, septic arthritis, and noninfectious inflammatory bone disease. False-negative bone scans occur and apparently do not correlate with the onset of disease, antibiotic therapy, causative organism, or radiographic changes. There can be definite radiographic evidence of osteomyelitis with no bone scan abnormality. Negative ^{99m}Tc scans reported in patients with documented osteomyelitis may reflect impaired blood supply to the infected area.

Indium-111 compounds have adequate agreement with clinical findings and a comparatively long half-life, allowing for the patient to be exposed to a significant radiation dose. In-111 images often are unavailable when required because imaging can be accomplished only after the 24-hour period (after injection) required for adequate In-111 localization. In-111 imaging is expensive and often fails to precisely define the extent of the infection [44].

Cost effectiveness Of all radionuclide scanning procedures, ^{99m}Tc scans are the most cost effective if a ^{99m}Tc generator and skilled personnel are available.

Emerging diagnostic procedures

- Several advances have been made in many of the diagnostic procedures. As discussed previously, MRI (through Gd-DPTA–enhanced T1-weighted images and STIR) and CT (through spiral CT scans) have increased the efficacy of these imaging modalities. However, most of the emerging diagnostic procedures have been found by nuclear medicine specialists.

Infecton (Draximage, Kirland, Canada)

This novel radionuclide uses radiolabeled ciprofloxacin to localize sites of infection. Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic that interacts with the bacterial DNA gyrase of gram-positive, gram-negative, and anaerobic bacterial species. Preliminary studies have been promising and Infecton has demonstrated reduced sensitivity for organisms with impermeable membranes to ciprofloxacin [49–51]. Infecton may not be effective to detect osteoarticular infections because of elevated levels of false-positives associated with nonspecific articular pooling of this radiopharmaceutical [52].

Radiolabeled polyclonal immunoglobulin G

These nonspecific antibodies may be radiolabeled and accumulate in areas of inflammation. The accumulation is secondary to vascular exudation into interstitial fluids without specific cell binding. Whereas polyclonal immunoglobulin G (labeled with ^{99m}Tc or In-111) shows sensitivity, the level of specificity depends on the type of infection (*ie*, low specificity in cases of pseudoarthrosis and joint replacement) [53].

Monoclonal antibodies

A ^{99m}Tc-labeled antigranulocyte monoclonal antibody Fab' fragment (LeukoScan; Immunomedics Inc., Morris Plains, NJ) had a higher sensitivity and specificity than In-111 WBC scintigraphy or ^{99m}Tc MDP in the detection of orthopaedic infections (long bone osteomyelitis, diabetic foot osteomyelitis, and prosthetic implant infection) [54]. Another monoclonal antibody in clinical trials is LeuTech (Palatin

Technologies Inc., Cranbury, NJ), a ^{99m}Tc-labeled murine immunoglobulin M monoclonal antigranulocyte antibody that binds to human polymorphonuclear leukocyte CD15 antigens [55]. This monoclonal antibody showed similar efficacy as 111-In–labeled leukocyte scintigraphy in the diagnosis of patients with appendicular skeletal osteomyelitis [56].

Although further studies are needed, this emerging diagnostic technique has good potential.

Chemotactic peptides

Technetium-99m or In-111 peptides (*eg*, N-formyl-methionyl-leucyl-phenylalanine) that are recognized by receptors on white blood cell subpopulations and induce chemotaxis have been shown to localize in areas of inflammation. Although new formulations and peptides have reduced the low specificity and toxic effects of these substances [57–59], their use in orthopaedic infections remains to be evaluated adequately.

Liposomes

Polyethylene glycol-containing liposomes can be labeled with lipophilic ^{99m}Tc or In-111 compounds. These liposomes can localize in abscess areas and have shown uptake in sterile and infectious inflammatory processes.

Nanocolloids

This imaging technology uses ^{99m}Tc-labeled albumin nanocolloids (< 50 nm diameter) that exude into the intravascular space. Although the sensitivity of nanocolloids is excellent and imaging can be administered within 1 hour after injection, the specificity is low because they collect in any area of infectious or sterile inflammation [60,61].

18-Fluorodeoxyglucose positron emission tomography imaging

The high sensitivity and specificity of 18-fluorodeoxyglucose positron emission tomography imaging for the detection of musculoskeletal infections, particularly in chronic cases, is well-documented [62,63]. However, this imaging technique cannot be used in the early postoperative phase [64]. Additional studies are needed to assess its ability to identify infections at the sites of total joint replacements and to distinguish infection from aseptic loosening of these prostheses.

Radiolabeled human recombinant interleukin-8

The human cytokine interleukin-8 (IL-8) is a powerful chemotactic factor that attracts polymorphonuclear leukocytes to sites of infection and inflammation. It was shown that human recombinant IL-8 radiolabeled with iodine-131 was able to specifically localize at osteomyelitis and cellulitis foci of infection [65].

Synthetic porphyrins

During investigations on the mechanisms of tumor localization of certain synthetic porphyrins, it was discovered that synthetic porphyrins accumulated at histamine receptors on basophils, neutrophils, mast cells, and eosinophils. These cells are involved in the acute inflammatory process. In preliminary studies, ^{99m}Tc tetraphenyl porphyrin sulfonate was able to localize areas of acute inflammation in an animal model of osteomyelitis [66]. However, additional studies need to be conducted.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
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