

Nuclear Medicine and the Infected Joint Replacement

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Nearly 700,000 hip and knee arthroplasties are performed annually in the United States. Although the results in most cases are excellent, implants do fail. Complications like heterotopic ossification, fracture, and dislocation are now relatively rare and easily diagnosed. Differentiating aseptic loosening, the most common cause of prosthetic joint failure, from infection, is important because their treatments are very different. Unfortunately, differentiating between these 2 entities can be challenging. Clinical signs of infection often are absent. Increased peripheral blood leukocytes, erythrocyte sedimentation rate, and C-reactive protein levels are neither sensitive nor specific for infection. Joint aspiration with Gram stain and culture is the definitive diagnostic test. Its specificity is in excess of 90%; its sensitivity is variable, however, ranging from 28% to 92%. Plain radiographs are neither sensitive nor specific and cross-sectional imaging modalities, such as computed tomography and magnetic resonance imaging, can be limited by hardware-induced artifacts. Radionuclide imaging is not affected by orthopedic hardware and is the current imaging modality of choice for suspected joint replacement infection. Bone scintigraphy is sensitive for identifying the failed joint replacement, but cannot be used to determine the cause of failure. Neither periprosthetic uptake patterns nor performing the test as a 3-phase study significantly improve accuracy, which is only about 50-70%. Thus, bone scintigraphy typically is used as a screening test or in conjunction with other radionuclide studies. Combined bone gallium imaging, with an accuracy of 65-80%, offers only modest improvement over bone scintigraphy alone. Presently, combined leukocyte/marrow imaging, with approximately 90% accuracy, is the radionuclide imaging procedure of choice for diagnosing prosthetic joint infection. In vivo leukocyte labeling techniques have shown promise for diagnosing musculoskeletal infection; their role in prosthetic joint infection has not been established. ¹¹¹In-labeled polyclonal immunoglobulin lacks specificity. ^{99m}Tc-ciprofloxacin does not consistently differentiate infection from aseptic inflammation. ¹⁸F-fluorodeoxyglucose positron emission tomography has been extensively investigated; its value in the diagnosis of prosthetic joint infection is debatable.

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Although joint arthroplasties were attempted in the nineteenth century, the era of modern joint replacement surgery, which has revolutionized the treatment of patients with advanced disorders of the hip and knee, began in earnest

approximately 50 years ago. Modern-day prostheses consist of metal, typically cobalt–chromium or titanium, and plastic, an ultrahigh molecular-weight polyethylene material (Fig. 1). These components can be attached to native bone with surgical cement, polymethylmethacrylate, by the application of a hydroxyapatite compound to their surface, or by constructing prosthetic materials with porous coating (Fig. 2). The latter 2 methods depend on new bone formation around the implanted hardware for fixation. The acetabular component of a hip arthroplasty can be press-fit, or forced into the acetabulum; surgical screws are used when necessary.¹ In well-secured cemented prostheses, the cement itself is in intimate contact with the endosteal bone. Normal marrow elements commonly are observed at the cement–bone interface. In well-fixed cementless porous-coated devices, the endosteal

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Figure 1 Contemporary prosthetic joints consist of metal (solid arrows) and ultrahigh molecular-weight polyethylene plastic (broken arrow). (Color version of figure is available online.)

bone is in direct contact with the prosthesis itself. Approximately 70% of the pore space is occupied by bone and the remainder by normal marrow elements. In the fixed nonporous coated type, well-organized paucicellular fibrous and collagenous tissue runs parallel to the prosthesis and usually is associated with partial mineralization.²

Nearly 700,000 hip and knee arthroplasties are performed annually in the United States.³ Although the clinical results of these procedures in the vast majority of cases are excellent, these implants do fail. Failures caused by heterotopic ossification, fracture, and dislocation are now relatively rare and usually can be diagnosed radiographically.⁴ Failure caused by aseptic loosening, however, has continued to increase in frequency. More than one-quarter of all prostheses eventually demonstrate evidence of loosening, often necessitating revision arthroplasty.¹ Although inappropriate mechanical load, fatigue failure at the bone prosthesis or cement–prosthesis interface, implant motion, and hydrodynamic pressure are sometimes responsible, the most frequent cause of aseptic loosening is an inflammatory reaction to one or more of the prosthetic components.⁵ Particulate debris, produced by component fragmentation, presumably attracts and activates tissue phagocytes normally present around the prosthesis. This debris is impervious to regular enzymatic destruction and frustrates the derivative function of the inflammatory cells, leading to repeated, futile attempts at phagocytosis. This in turn stimulates secretion of proinflammatory cytokines and proteolytic enzymes that damage bone and cartilage and activate immune cells. The heightened inflammatory response leads to osteolysis, causing loss of supporting osse-

ous tissues and, eventually, loosening of the prosthesis. Histopathologically, a synovial-like pseudomembrane develops. The cellular composition of this pseudomembrane is variable: histiocytes are the most commonly identified cell (95% of specimens), followed by giant cells (80%), and lymphocytes and plasma cells (25%). Neutrophils are present in less than 10% of the cases.^{6–8}

Infection, although uncommon, is perhaps the most serious complication of joint arthroplasty surgery, ranging in frequency from about 1% to 2% for primary implants, to about 3% to 5% for revision implants. Approximately one-third of prosthetic joint infections develop within 3 months, another one-third within 1 year, and the remainder more than 1 year after surgery. Histopathologically, the inflammatory reaction that accompanies the infected prosthesis can be similar to that present in aseptic loosening, with one important difference: neutrophils, which usually are absent in aseptic loosening, are invariably present in large numbers in infection.^{1,9}

The treatment of infected hardware often requires multiple admissions. An excisional arthroplasty, or removal of the prosthesis, is performed, followed by a protracted course of antimicrobial therapy. A revision arthroplasty eventually is performed. Aseptic loosening, in contrast, usually is managed with a single-stage exchange arthroplasty requiring only 1 hospital admission and 1 surgical intervention.^{1,10}

Because their treatments are so different, distinguishing infection from aseptic loosening of a prosthesis is extremely important. A test that is sensitive but not specific will lead to multiple, expensive, operations in patients in whom a single intervention may have sufficed. The specific, but insensitive, test also results in additional surgical intervention because undiagnosed infection will cause any revision implant to fail. Unfortunately, differentiating aseptic loosening from infection can be challenging. Clinical signs of infection often are



Figure 2 Porous coated acetabular component. These components rely on bony in growth into the minute crevices on their surface for immobilization. Screws can be used for additional bony anchorage. Note the hole at the top (arrow). (Color version of figure is available online.)

absent. Increased peripheral blood leukocytes, erythrocyte sedimentation rate, and C-reactive protein levels are neither sensitive nor specific for infection. Joint aspiration with Gram stain and culture is considered the definitive diagnostic test; its sensitivity, however, is variable, ranging from 28% to 92%. Its specificity is more consistent, ranging from 92% to 100%.^{1,11} Among the various imaging studies, plain radiographs are neither sensitive nor specific and cross-sectional imaging modalities, such as computed tomography and magnetic resonance imaging, can be limited by hardware induced artifacts. Radionuclide imaging is not affected by metallic hardware and is the current imaging modality of choice for evaluation of suspected joint replacement infection.¹

Bone Scintigraphy

Bone scintigraphy, which is widely available and easily performed, is extremely sensitive for detecting bone remodeling changes around prosthetic joints and its role in the evaluation of the painful replacement has been extensively investigated over the years. Most investigations have found that the test is sensitive for identifying the failed joint replacement but cannot determine the cause of failure. Gelman and coworkers¹² reviewed the results of bone scintigraphy performed on 21 painful joint replacements, including 17 hip and 4 knee prostheses. They reported an accuracy of 85% in the hips and 100% in the knees for this technique. Weiss and coworkers,¹³ using focally increased uptake at the tip of the femoral component or in the region of the acetabular component as the criterion for an abnormal study, reported that bone scintigraphy was 100% sensitive and 77% specific for diagnosing infection or loosening of the total hip replacement.

Some investigators have attempted to differentiate aseptic loosening from infection of hip prostheses by analyzing periprosthetic uptake patterns. Williamson and coworkers¹⁴ found that focal periprosthetic uptake was associated with aseptic loosening, whereas diffuse uptake around the femoral and acetabular components was associated with infection (Fig. 3). Williams and coworkers,¹⁵ however, found that diffusely increased activity was associated with both aseptic loosening and infection (Fig. 4). Mountford and coworkers¹⁶ reported that diffuse periprosthetic uptake was reasonably specific, but not sensitive for infection. Aliabadi and coworkers¹⁷ reported that bone scintigraphy accurately diagnosed prosthetic loosening but could not distinguish the aseptically loosened from the loosened, infected prosthesis. Lieberman and coworkers¹⁸ reported that bone scintigraphy was sensitive and specific for identifying loosened hip replacements, but excluded infected devices from their analysis.

Increased periprosthetic activity on bone images reflects increased bone mineral turnover, which can result from any of a number of conditions besides infection. This problem is further complicated by the numerous patterns of periprosthetic uptake associated with asymptomatic hip and knee replacements. During the first year after implantation of a total hip replacement, periprosthetic uptake patterns are very variable; subsequently, in the case of the cemented hip replacement, most asymptomatic patients will have a normal

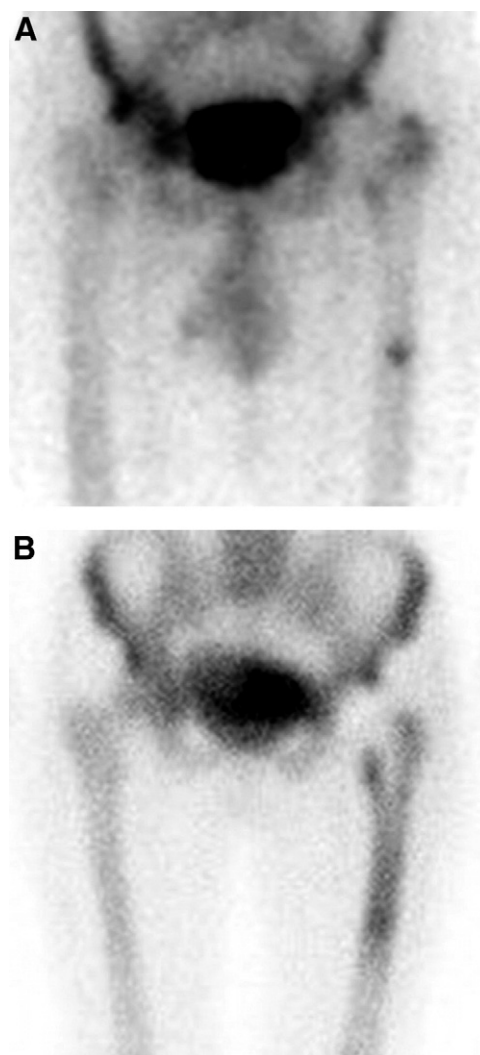


Figure 3 (A) Anterior bone scan image shows focally increased activity at the tip of the femoral component of a left hip replacement, a pattern often thought to be consistent with aseptic loosening. (B) Anterior bone scan image shows diffusely increased activity around the femoral component of a left hip replacement, a pattern often thought to indicate infection.

scan, ie, one in which periprosthetic activity is indistinguishable from adjacent, normal, nonarticular bone (Fig. 5). Up to 10% of asymptomatic patients, however, will have persistent periprosthetic uptake beyond this time.¹⁹ In the case of the porous-coated hip replacement, persistent uptake beyond 1 year is even more prevalent.^{20,21} The use of hybrid, bipolar, and hydroxyapatite-coated devices further complicates matters because few data are available about the evolution of normal periprosthetic uptake patterns around these devices.

Assessment of the total knee replacement with bone scintigraphy also is problematic, with more than 60% of femoral components and nearly 90% of tibial components demonstrating persistent periprosthetic activity more than 12 months after implantation.²²⁻²⁴ Hofmann and coworkers²⁴ studied asymptomatic knee replacements with serial bone scans during the course of 2 years and found that, although periprosthetic uptake generally decreased over time, there

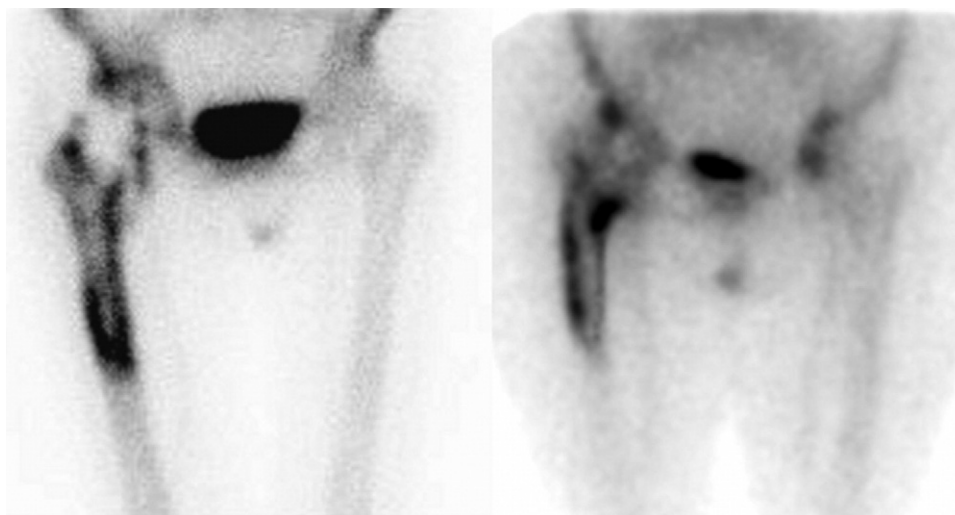


Figure 4 There is diffusely increased activity around the femoral component of an infected right hip replacement (left) and around an aseptically loosened right hip replacement (right). Bone scintigraphy does not reliably differentiate infection from aseptic loosening.

was considerable patient-to-patient variation. They concluded that sequential scans are needed to determine the significance of increased periprosthetic uptake (Fig. 6). Palestro and coworkers²⁵ found that bone scintigraphy was neither sensitive nor specific for diagnosing the infected total knee replacement. Love and coworkers²⁶ recently reported similar results.

The accuracy of this test is not improved when one performs 3-phase bone scintigraphy (Fig. 7). Magnuson and coworkers²⁷ reviewed 49 painful lower-extremity joint replacements and found that 3-phase bone scintigraphy was 100% sensitive, 18% specific, and 53% accurate for diagnosing infection. Levitsky and coworkers,²⁸ in an investigation of 72 joint replacements, reported a sensitivity of 30%, specificity of 86%, and an accuracy of 68%. Palestro and cowork-

ers²⁵ found that the 3-phase bone scan was neither sensitive (67%) nor specific (76%) for diagnosing the infected knee replacement. Love and coworkers²⁶ recently reviewed the results of 3-phase bone scintigraphy performed on 150 lower-extremity joint replacements, including 96 hip and 54 knee prostheses, and reported that the test was 76% sensitive and 51% specific for diagnosing infection. The accuracy of the test was 62%, greater than the 50% accuracy of bone scintigraphy, but still very low.

The overall accuracy of radionuclide bone imaging in the evaluation of the painful prosthetic joint is about 50-70%, too low to be clinically useful, except perhaps as a screening test, or in conjunction with other radionuclide studies like gallium or labeled leukocyte imaging.

Bone/Gallium Imaging

Although the propensity of gallium-67 to accumulate in infection and inflammation was recognized nearly 40 years ago, it was not until the late 1970s that extensive investigations of its role in musculoskeletal infection commenced. Reing and coworkers²⁹ evaluated 79 joint replacements with both bone and gallium scintigraphy. Bone scintigraphy was abnormal in all 20 (100% sensitivity) infected prostheses, but also was abnormal in 50 uninfected prostheses, rendering it very non-specific (15%). In contrast, when using gallium, the authors were able to identify 19 of 20 infected prostheses (95% sensitivity). Its results were negative in all 59 uninfected devices (100% specificity). These authors concluded that performing gallium imaging in addition to bone scintigraphy greatly enhances the accuracy of the radionuclide diagnosis of the infected joint replacement. Rushton and coworkers³⁰ reported that all 13 patients with an infected hip prosthesis demonstrated abnormal periprosthetic accumulation of gallium, whereas none of 18 patients with aseptically loosened devices demonstrated abnormal periprosthetic activity (100% accu-

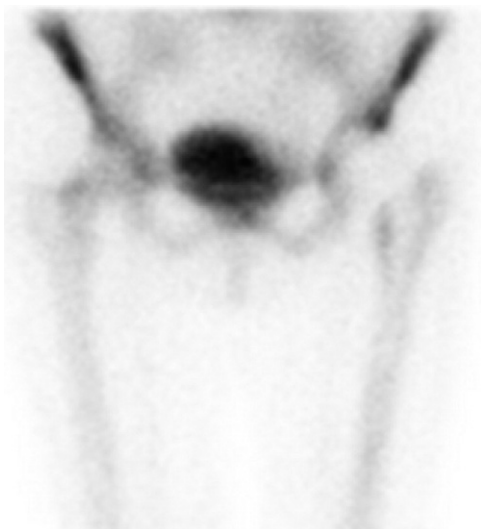


Figure 5 Normal bone scan of a left total hip replacement. Periprosthetic activity is indistinguishable from adjacent nonarticular bone activity.



Figure 6 (A) Bilateral total knee replacements. The right knee replacement is asymptomatic, the left is infected. (B) Bilateral total knee replacements. The right knee replacement is aseptically loosened, the left is asymptomatic. Periprosthetic activity around knee replacements is very variable. As these images demonstrate, it may not be possible, on the basis of a single bone scan, to differentiate aseptic loosening from infection from normal postoperative appearance.

racy). McKillop and coworkers³¹ reported that gallium images were abnormal in 5 of 6 infected joint replacements and normal in 7 of 9 uninfected prostheses (80% accuracy). Mountford and coworkers¹⁶ also found that the accuracy of gallium scintigraphy for diagnosing prosthetic hip infection was about 80%. Aliabadi and coworkers¹⁷ reported that gallium scintigraphy was only 37% sensitive but 100% specific for diagnosing prosthetic hip infection.

Gallium accumulates in both septic and aseptic inflammation, as well as in the bone marrow, and in areas of increased bone mineral turnover in the absence of infection. In an effort to improve the accuracy of both bone and gallium imaging, the 2 studies are often interpreted together, according to standardized criteria.³² The test is positive for osteomyelitis when distribution of the 2 tracers is spatially incongruent or, when the distribution is spatially congruent and the relative intensity of gallium uptake exceeds that of the diphospho-

nate (Fig. 8). The test is equivocal for osteomyelitis when the distribution of the 2 radiotracers is congruent, both spatially and in terms of intensity (Fig. 9). The test is negative for osteomyelitis when the gallium images are normal, regardless of the bone scan findings or when the distribution of the 2 tracers is spatially congruent and the relative intensity of gallium uptake is less than that of the diphosphonate (Fig. 10).

Interpreting bone and gallium images together has not resulted in a marked improvement in accuracy over either study alone. Tehranzadeh and coworkers³³ reported a 95% accuracy for the combined study; most other investigators, however, have reported less satisfactory results. Williams and coworkers¹⁵ identified abnormal gallium uptake in 13 (93%) of 14 infected joint replacements and in only 2 (8%) of 24 uninfected joint replacements. When they evaluated combined bone/gallium scintigraphy, however, they found that only 7 (50%) of the 14 infected joint replacements demonstrated spatially incongruent bone gallium images; in the other 7 infected joint replacements, the images were spatially congruent. Merkel and coworkers³⁴ found that the sensitivity, specificity, and accuracy of the technique for diagnosing joint replacement infection in an animal model, were 61%, 71%, and 67%, respectively. In 130 patients with painful orthopedic prostheses, these investigators reported that bone/gallium imaging was 66% sensitive, 81% specific, and 77% accurate for diagnosing infection.³⁵ Gomez-Luzuriaga and coworkers³⁶ reported a sensitivity, specificity, and accuracy of 70%, 90%, and 80%, respectively, for bone/gallium imaging. Kraemer and coworkers³⁷ reported a low sensitivity (38%), and a very high specificity (100%) for bone/gallium imaging for diagnosing prosthetic hip infection. The overall accuracy of the test was 81%. Love and coworkers²⁶ recently reported that bone/gallium imaging was 75% sensitive, 59% specific, and 66% accurate for diagnosing prosthetic joint infection. Combined bone/gallium imaging, with an accuracy of about 65-80%, offers only a modest improvement over bone scintigraphy alone.

Labeled Leukocyte Imaging

Labeled leukocyte imaging should be well suited for diagnosing the infected joint replacement because white cells usually do not accumulate at sites of increased bone mineral turnover in the absence of infection. The results reported, however, have been both inconsistent and disappointing. Propst-Procator and coworkers³⁸ found the technique was sensitive and specific for detecting acute musculoskeletal infection, including infected joint replacements. Noninfectious conditions such as heterotopic ossification, metastatic disease, and degenerative arthritis did not accumulate labeled white cells. Pring and coworkers,³⁹ using labeled granulocytes to evaluate 50 prosthetic joints, including 11 that were infected, reported a sensitivity of 100% and a specificity of 89.5% for this technique. In this investigation, studies in which periprosthetic white cell activity was at least as intense as normal marrow activity were classified as positive for infection. Magnuson and coworkers,²⁷ using similar criteria, reported a sensitivity and specificity of 88% and 73%, respectively, for diagnosing infected orthopedic hardware.

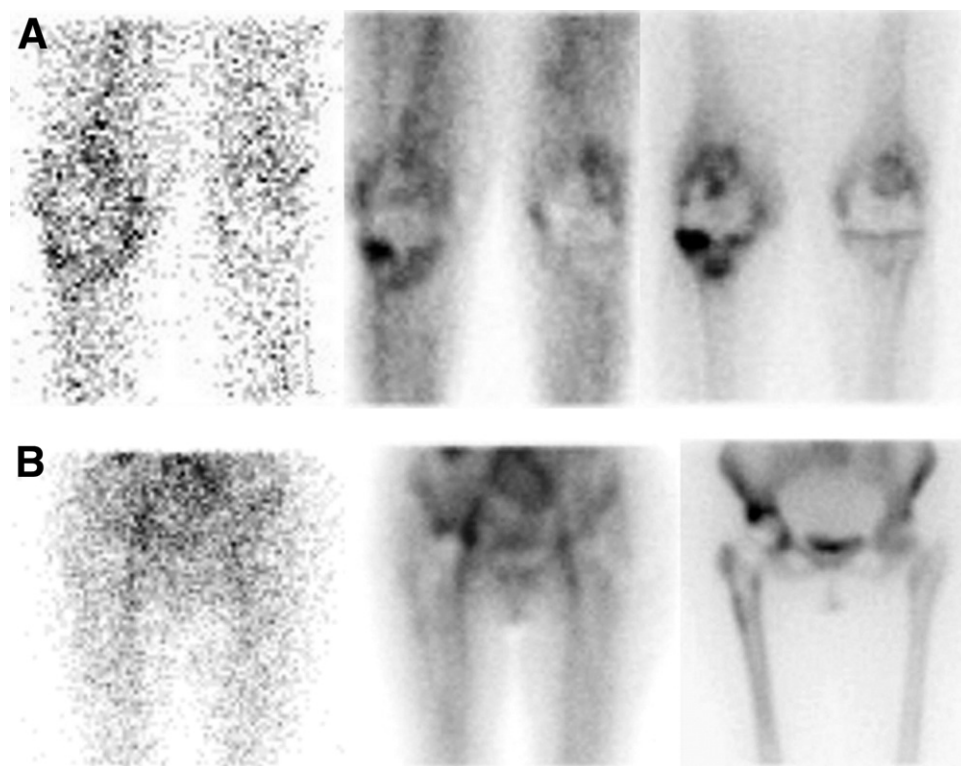


Figure 7 (A) Aseptically loosened right total knee replacement. The bone scan is positive in all 3 phases. (B) Infected right total hip replacement. The first 2 phases of the bone scan are completely normal; on the third phase, there is mildly increased activity along the proximal lateral aspect of the femoral component. Performing it as a 3-phase study does not improve the accuracy of bone scintigraphy for diagnosing prosthetic joint infection.

McKillop and coworkers³¹ studied 15 painful prostheses, including 6 that were infected. They reported sensitivities and specificities of 50% and 100%, respectively, for leukocyte imaging compared with 86% and 82%, respectively, for gallium. They concluded that the low sensitivity of labeled leukocyte imaging was caused by the chronic, low-grade inflammations present in their population. Wukich and coworkers,⁴⁰ as part of a larger series, evaluated 24 joint replacements. Classifying images as positive for infection when focally increased activity, compared with adjacent bone activity, was identified, they reported that labeled leukocyte imaging was 100% sensitive, but only 45% specific for joint replacement infection. Johnson and coworkers⁴¹ evaluated hip replacements and also reported a high sensitivity (100%) and a low specificity (50%) for this technique. Using any periprosthetic activity, regardless of intensity, as the criterion for infection, Palestro and coworkers⁴² reported that labeled leukocyte imaging was 100% sensitive, but only 23% specific for diagnosing prosthetic hip infection. When periprosthetic activity more intense than the contralateral hip activity was used as the criterion for a positive study, the sensitivity fell to 23%, and the specificity increased to 63%. In an investigation of knee replacements, using any periprosthetic activity, regardless of intensity, as the criterion for infection, they found that the sensitivity and specificity of the test were 89% and 50%, respectively. Using only periprosthetic activity more intense than the contralateral knee activity as the criterion for a positive study, the sensitivity was unchanged at 89%, while the specificity rose to 75%.²⁵

Poor sensitivity of labeled leukocyte imaging for diagnosing prosthetic joint infection has been attributed to the chronic nature of the process, ie, presumably the neutrophilic response has ceased, or at least waned, by the time the patient undergoes labeled leukocyte imaging. Neutrophils are invariably present in the infected joint replacement, regardless of the duration of symptoms and chronicity is not, therefore, a suitable explanation for low sensitivity. Poor specificity often has been attributed to non specific inflammation. Inflammation in an aseptically loosened joint replacement is not neutrophil-mediated, and the relative insensitivity of labeled leukocyte imaging for detecting other than neutrophil mediated inflammations is well known.⁴³ False-positive results cannot, therefore, be attributed solely to inflammation.

The explanation of the often-contradictory results reported for labeled leukocyte imaging is related primarily to an inability to develop a satisfactory method for interpretation of the images. Labeled white cell images usually are interpreted by comparing intensity of uptake in the region of interest to the intensity of uptake in some predefined reference point. In the case of the prosthetic joint, the reference point selected usually is the bone marrow. Those studies in which uptake of labeled leukocytes in the region of interest exceeds uptake in the normal reference point are classified as abnormal or positive for infection. A prerequisite for the success of the procedure is that, when infection is present, uptake in the region of interest exceeds uptake in the reference point. Conversely, in the absence of infection, intensity of uptake in the region of interest should not exceed that in the reference point.¹ Unfortunately, the intensity of peripros-

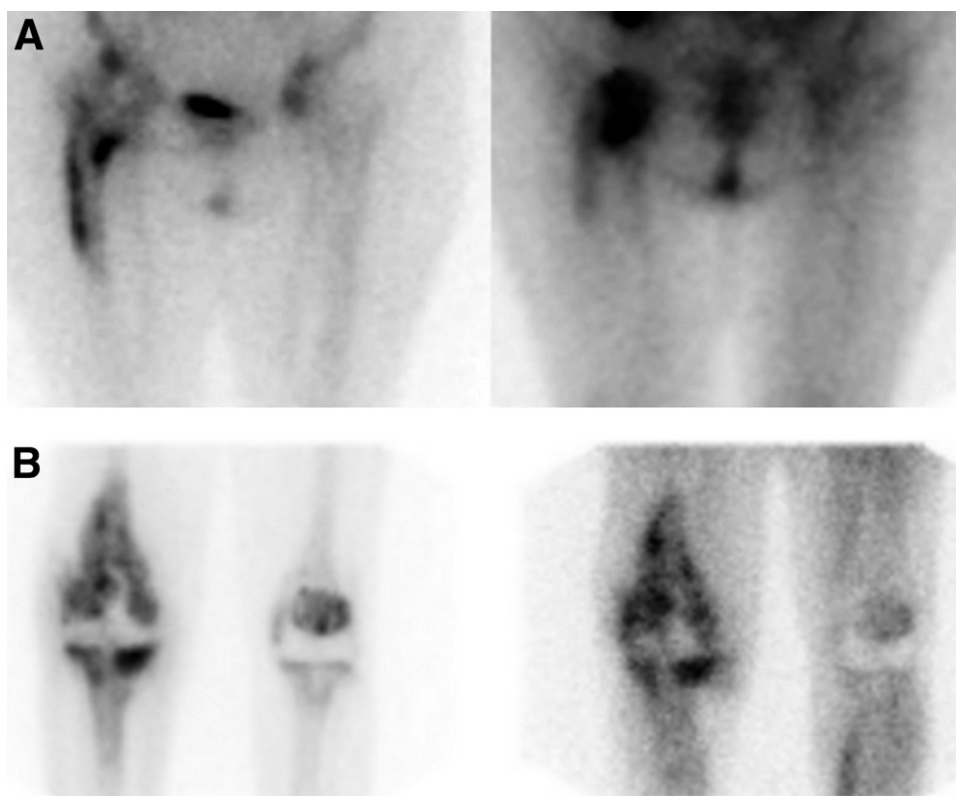


Figure 8 (A) Positive bone/gallium study. There is spatially incongruent distribution of activity. On the bone scan (left), there is increased activity around the femoral component (same patient in Fig. 4, right) whereas on the gallium scan (right), abnormal uptake is confined primarily to the hip joint. (B) Positive bone/gallium study. The periprosthetic distribution of activity is spatially congruent on the bone (left) and gallium (right) images, but is more intense on the gallium image.

thetic labeled leukocyte activity is not related to the presence or absence of infection (Fig. 11).

There is a second, even more fundamental problem with labeled leukocyte imaging. Although the normal distribution of hematopoietically active marrow in adults is confined to the axial skeleton and proximal humeri and femurs, there is considerable interindividual variation. Generalized marrow expansion is a response to a systemic process, such as sickle

cell disease, neoplasm, and other myelophthistic states. Localized marrow expansion is a response to a local stimulus, such as fracture, orthopedic hardware, the neuropathic joint and even calvarial hyperostosis (Fig. 12).⁴⁴⁻⁴⁶ Both generalized and localized marrow expansion can alter the “normal” distribution of marrow making it difficult to separate uptake of labeled leukocytes in atypically located, but otherwise normal, marrow from uptake in infection.⁴⁴

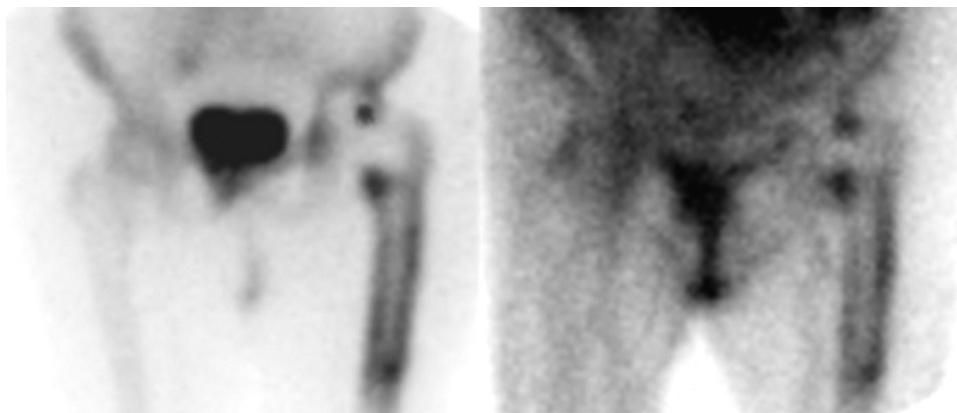


Figure 9 Equivocal bone/gallium study. The periprosthetic distribution of activity on bone (left) and gallium (right) images is virtually identical, both spatially and in intensity.

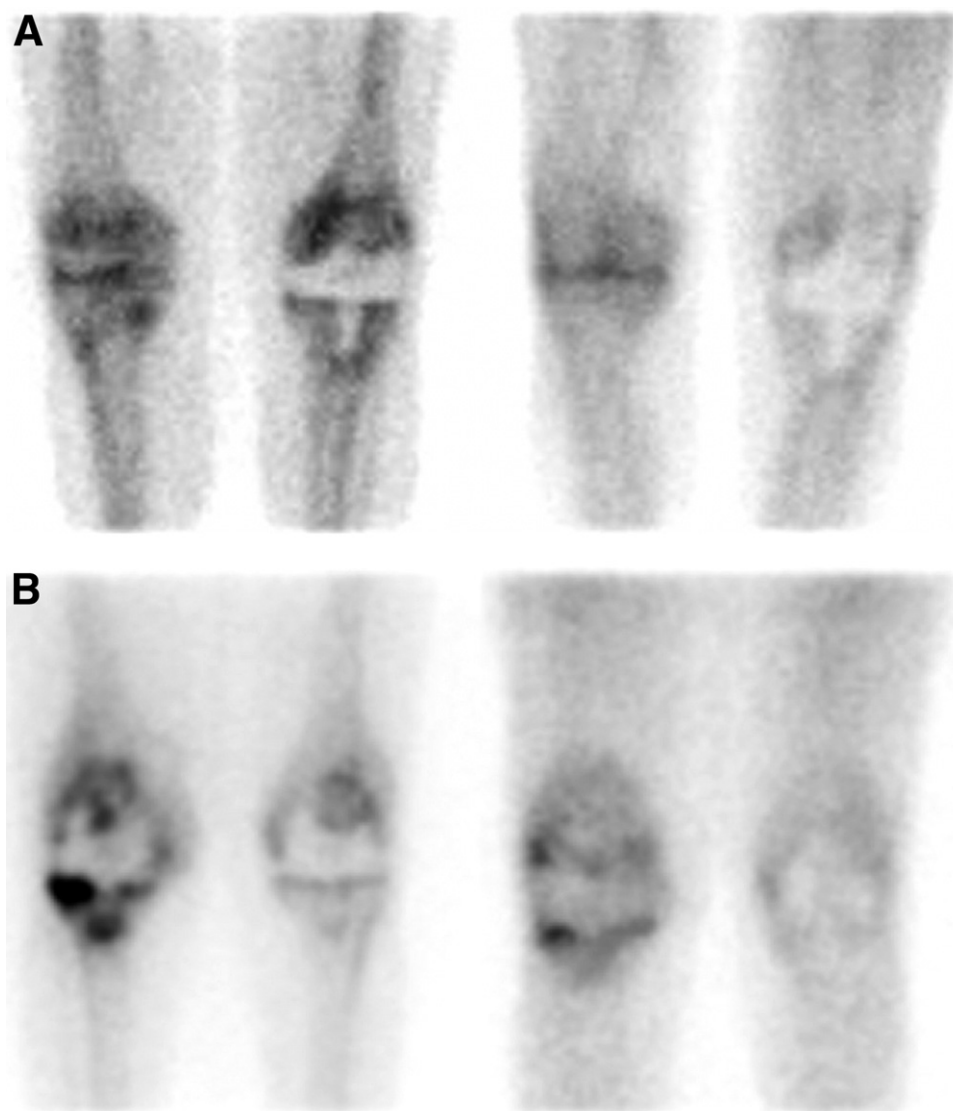


Figure 10 (A) Negative bone/gallium study. There is mildly increased periprosthetic activity around a left total knee replacement on the bone scan (left). The gallium scan (right) is completely normal. (B) Negative bone/gallium study. The distribution of activity around the right knee prosthesis is spatially congruent on the bone (left) and gallium (right) images. The intensity of uptake on the gallium image is considerably less than that on the bone scan.

Leukocyte/Bone Imaging

Some investigators have reported that combined leukocyte/bone imaging is superior to leukocyte imaging alone for diagnosing prosthetic joint infection. Wukich and coworkers⁴⁰ reported that the specificity rose from 45% for leukocyte imaging alone to 85% for leukocyte–bone imaging, although the sensitivity dropped from 100% to 85%. Johnson and coworkers⁴¹ reported similar results in the assessment of total hip arthroplasties, noting that the combined technique offered a greater specificity (95% versus 50%) at the expense of a somewhat lower sensitivity (88% versus 100%).

Other investigators have found the test to be less accurate. Palestro and coworkers²⁵ studied painful total knee replacements and reported that the sensitivity (67%) and

specificity (78%) of leukocyte–bone imaging were not any better than those of leukocyte imaging alone (89% sensitivity and 75% specificity). Love and coworkers²⁶ found that leukocyte/bone imaging was only slightly more accurate (70%) than leukocyte imaging alone (64%) for diagnosing the infected joint replacement. Oswald and coworkers²⁰ observed incongruent leukocyte/bone images in 15% of asymptomatic patients with porous-coated hip arthroplasties and concluded that, in patients with this type of hip replacement, incongruence of activity at the prosthetic tip is of little clinical utility.

Diphosphonates accumulate in bone, while labeled leukocytes accumulate in marrow. Conditions that affect marrow may or may not affect bone and vice versa (Fig. 13). Even when a particular entity affects both bone and marrow, the effects may be dramatically different.⁴⁷

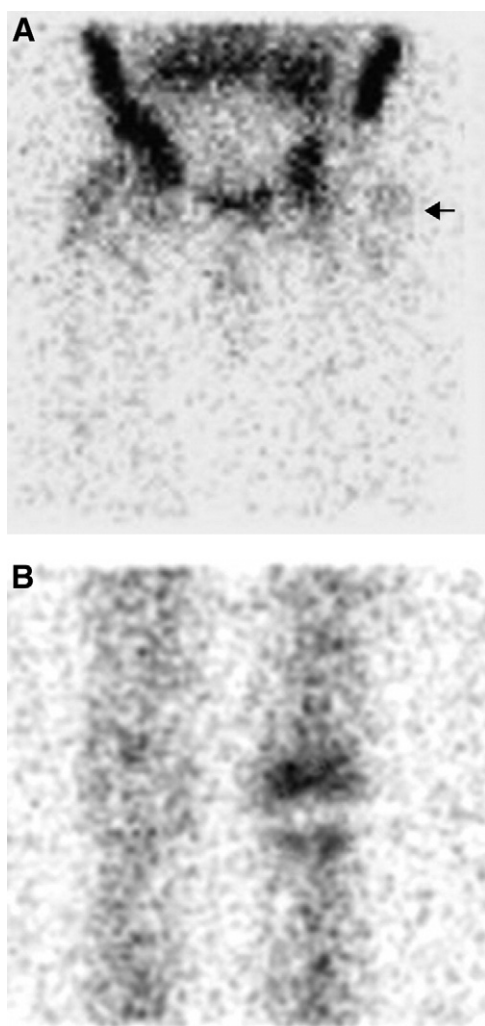


Figure 11 (A) Infected left hip replacement. Anterior-labeled leukocyte image shows faint periprosthetic activity (arrow) that is considerably less intense than activity in the contralateral hip or adjacent marrow activity. (B) Aseptically loosened left total knee replacement. There is intense periprosthetic accumulation of labeled leukocytes around the prosthesis. Intensity of labeled leukocyte accumulation is not a reliable criterion for diagnosing prosthetic joint infection. Compare this image to (A).

Leukocyte/Marrow Imaging

Labeled leukocyte and bone marrow images both reflect radiotracer accumulation in the reticuloendothelial cells, or fixed macrophages, of the marrow. The distribution of marrow activity is similar on leukocyte and bone marrow images in normal individuals as well as in those with underlying marrow abnormalities, i.e., the images are spatially congruent. The one exception to this congruent pattern is osteomyelitis, which stimulates uptake of white cells but suppresses uptake of sulfur colloid. Unlike other conditions that affect the marrow, in osteomyelitis, leukocyte and marrow images are dissimilar or spatially incongruent (Fig. 14).⁴⁸

Mulamba and coworkers⁴⁹ reported a sensitivity of 92% and a specificity of 100% for diagnosing infected hip replacements with leukocyte/marrow imaging. Palestro and coworkers⁴² investigated leukocyte/marrow imaging in 50 patients

with painful total hip replacements and found that the study was 100% sensitive and 97% specific for diagnosing infection. In another study, these investigators found that leukocyte/marrow imaging was equally satisfactory for the evaluation of painful knee prostheses and was superior to bone scintigraphy (including 3-phase) alone, leukocyte imaging alone and leukocyte/bone imaging.²⁵ In a review of 59 failed lower-extremity joint replacements, all with surgically, histopathologically and microbiologically confirmed diagnoses, Love and coworkers⁵⁰ reported that the sensitivity, specificity, and accuracy of leukocyte/marrow imaging for diagnosing prosthetic joint infection were 100%, 91%, and 95%, respectively.

Although most investigations have found that leukocyte/marrow imaging accurately diagnoses the infected joint replacement, some investigations have raised concerns about the sensitivity of the test. Pill and coworkers⁵¹ reported that leukocyte/marrow imaging detected only 5 of 10 infected prostheses for a sensitivity of only 50%. Their explanation for the low sensitivity was that most of these infections are subacute or chronic, and the dominant cells are lymphocytes and monocytes, rather than neutrophils. In fact, however, neutrophils are invariably present, usually in large numbers, regardless of the duration of the infection. Thus the explanation for the poor sensitivity in this investigation is uncertain. Unfortunately, no illustrations were provided. Joseph and coworkers⁵² reported that although it was 100% specific, leukocyte/marrow imaging was only 46% sensitive for diagnosing prosthetic joint infection. Adding a “flow phase” to the marrow portion of the study, improved the sensitivity to 66%, with only a slight decrease in specificity to 98%. The reasons for the low sensitivity of the test compared with previous investigations, according to the investigators, were related to lack of operative confirmation in all cases, and insufficient length of clinical follow-up in previous studies. There are, however, other equally important differences be-

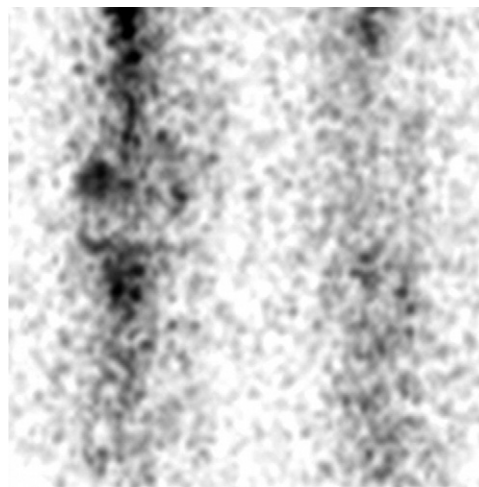


Figure 12 Labeled leukocyte activity around an uninfected right total knee replacement is caused by the presence of bone marrow, not by infection. Localized marrow expansion can, as this example illustrates, confound study interpretation.

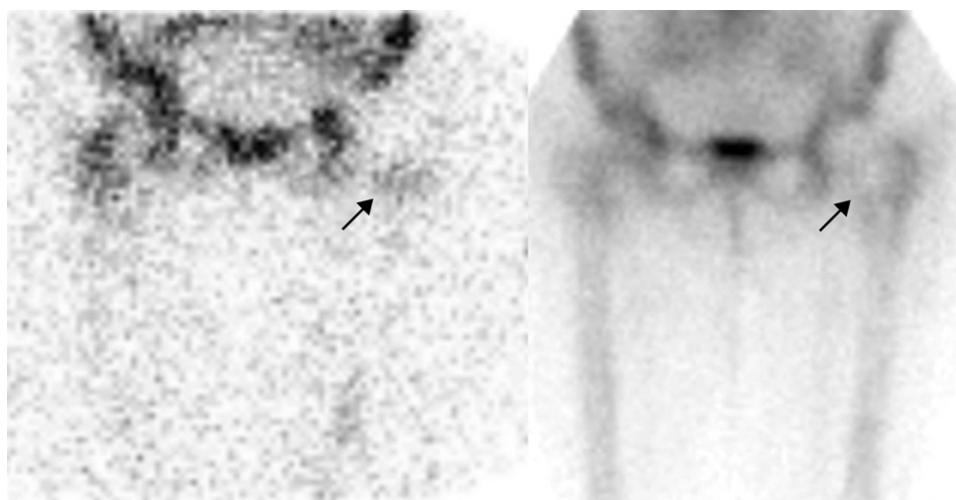


Figure 13 Aseptically loosened left hip replacement. There is spatially incongruent distribution of activity on the labeled leukocyte and bone images (arrows), and the study is (false) positive for infection.

tween this and previous investigations. These investigators used 10 uCi, rather than 10 mCi, of ^{99m}Tc -sulfur colloid. No information on the quality of the sulfur colloid preparation was given, leukocytes were sent to an outside radiopharmacy for labeling, and images were interpreted by a bone radiologist, with no indication of this individual's experience in radionuclide imaging. Interestingly, as with the investigation of Pill and coworkers,⁵¹ although poor sensitivity was the salient finding in this investigation, no examples of false negative studies were provided.

More recently, Love and coworkers²⁶ reported on 150 failed joint prostheses with surgically, histopathologically and microbiologically confirmed final diagnoses. In this investigation the sensitivity, specificity, and accuracy of leukocyte/marrow imaging were 96%, 87%, and 91%, respectively. The test was significantly more accurate than bone (50%), bone/gallium (66%), and leukocyte/bone imaging (70%) in their population. These results confirm the sensitivity and specificity of leukocyte/marrow imaging for diagnosing prosthetic joint infection as well as its superiority over other radionuclide tests.

Meticulous technique is critical to the success of leukocyte/marrow imaging. When the study is performed with ^{111}In -labeled leukocytes, marrow imaging can be performed before or after the leukocyte study. Performing marrow imaging after the leukocyte study has some advantages. If there is no labeled leukocyte activity around the prosthesis, marrow imaging need not be performed. With modern imaging equipment, simultaneous dual-isotope acquisitions can be performed. This permits more precise comparison of leukocyte and marrow images, as well as direct computer superimposition of one image on another, facilitating study interpretation. Sulfur colloid should be freshly prepared, ideally just before use. Using sulfur colloid that is more than about one to two hours old results in images of inferior quality, with increased background and, often, considerable urinary bladder activity, which is especially troublesome when studying the hip.⁴⁸

If ^{99m}Tc -labeled leukocytes are used, simultaneous dual isotope imaging is, of course, not possible. When one uses ^{99m}Tc -labeled leukocytes, persistent, and potentially confounding, activity on the leukocyte images can persist for up to 48 hours after injection and therefore it is best to allow an interval of at least 72 hours between the 2 phases of the study.⁴⁸

Pelosi and coworkers⁵³ have suggested that, by acquiring labeled leukocyte images at multiple time points, it may be possible to avoid performing bone marrow scintigraphy. Early images are thought to reflect labeled leukocyte uptake in marrow while late images are thought to reflect labeled leukocyte uptake in infection. Incongruence between early and late images is indicative of infection. With the use of visual analysis, the accuracy of this dual time-point imaging was only about 75%; with the use of semiquantitative analysis, the accuracy improved to about 95%. Unfortunately only about half the patients in this series had surgical confirmation of their diagnosis, and therefore the true merits of this technique await further investigation.

^{18}F -Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

Despite its utility, there are significant disadvantages to leukocyte/marrow scintigraphy. The *in vitro* labeling process is labor intensive, not always available, and requires direct contact with blood products. The need to perform marrow imaging adds to the complexity and cost of the study and is an additional inconvenience to patients, many of whom are elderly and debilitated. Thus, investigators continue to search for suitable alternatives. One agent that has generated considerable interest for diagnosing prosthetic joint infection is ^{18}F -FDG. The high-resolution tomographic images, availability of the agent, and rapid completion of the procedure are all desirable traits. Published results to date, however, are inconclusive.^{50-52,54-58}

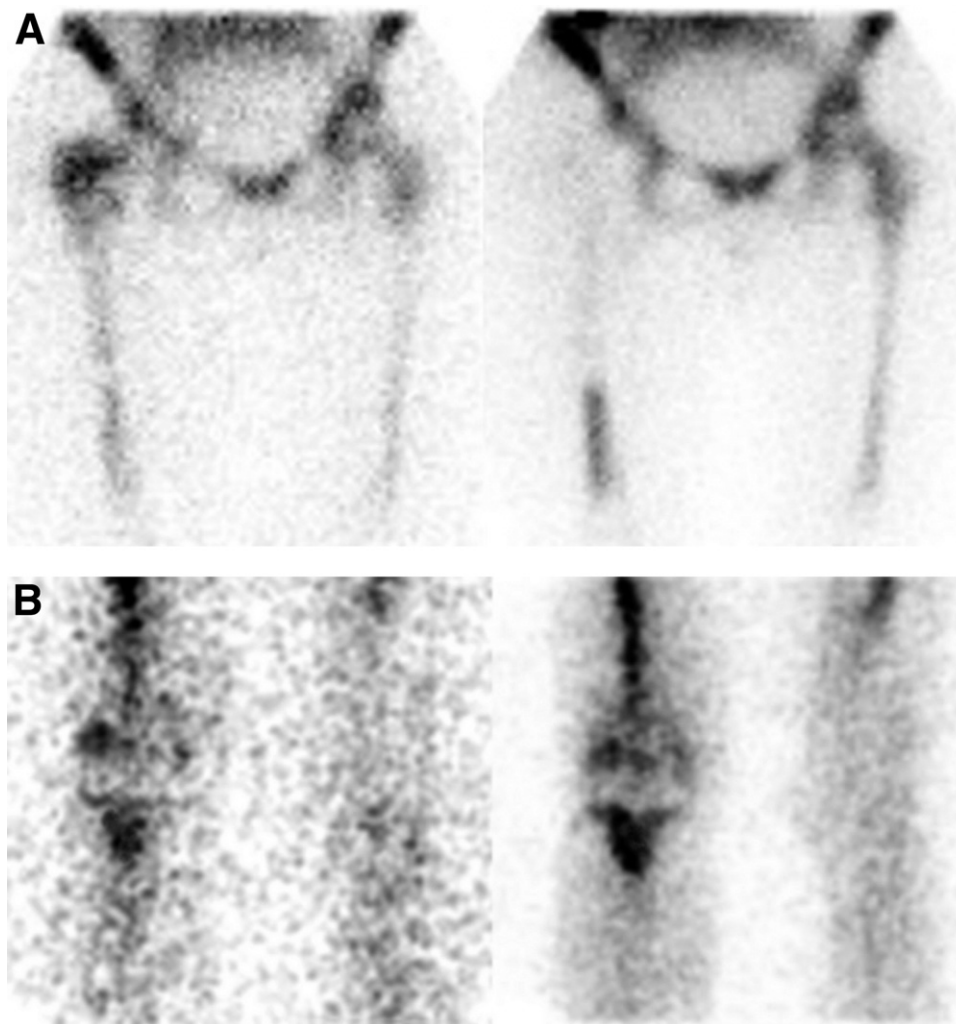


Figure 14 (A) Infected right hip replacement. The distribution of activity around the right hip prosthesis on labeled leukocyte (left) and marrow (right) images is spatially incongruent. In this case labeled leukocyte activity around the prosthesis is due to infection. (B) Aseptically loosened right total knee replacement. There is intense periprosthetic activity on both the labeled leukocyte image (left) and marrow (right) images, and the combined study is negative for infection. In this case labeled leukocyte accumulation around the prosthesis is caused by localized marrow hyperplasia, not by infection. (Same patient as shown in Fig. 12.)

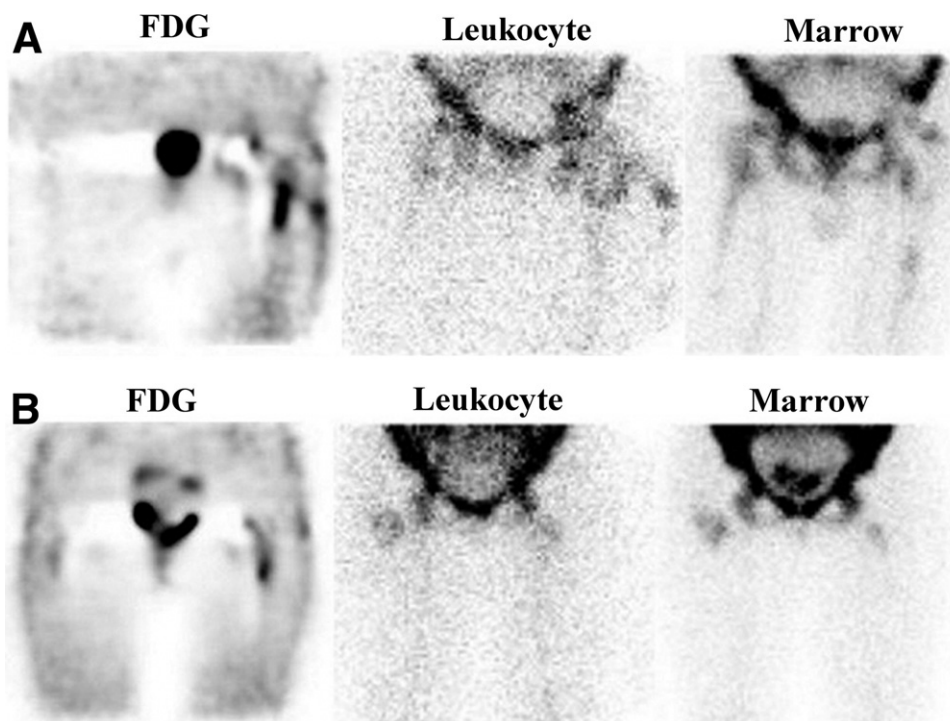
Zhuang and coworkers⁵⁴ evaluated FDG-PET in 74 joint prostheses, 21 of which were infected. Studies were considered positive for infection when an area of increased uptake was identified at the bone prosthesis interface. They reported a sensitivity, specificity, and accuracy of 90%, 89.3%, and 89.5%, respectively, for prosthetic hip infection, and sensitivity, specificity, and accuracy of 90.9%, 72%, and 77.8%, respectively, for prosthetic knee infection. These investigators also found that the accuracy of the test depended on location, not intensity, of FDG uptake. In a series of 41 painful hip arthroplasties, Chacko and coworkers⁵⁵ reported that the presence of bone prosthesis interface activity along the shaft of the femoral component of a hip replacement was 92% sensitive and 97% specific for infection. They found that intensity of uptake was not useful for separating the infected from the aseptically loosened device. In agreement with Zhuang and coworkers⁵⁴ and Chacko and coworkers,⁵⁵ Reinartz and coworkers⁵⁶ found that activity around the acetab-

ular component and proximal aspect of the femoral component of hip replacements was not associated with infection. These investigators also found that periprosthetic uptake patterns on PET images were useful for differentiating infection from aseptic loosening, whereas intensity of uptake was not.

Manthey and coworkers⁵⁷ studied 28 prostheses, 14 hip and 14 knee, with FDG-PET. These investigators reported that the test was 96% accurate and, by analyzing both intensity and patterns of periprosthetic uptake, it was possible to accurately differentiate among aseptic loosening, synovitis, and infection. They also reported that activity around the femoral head and neck indicated the presence of synovitis plus infection. Their findings thus contradict those of Zhuang and coworkers,⁵⁴ Chacko and coworkers,⁵⁵ and Reinartz and coworkers.⁵⁶

Stumpe and coworkers⁵⁸ performed FDG-PET on 35 painful hip prostheses, including 9 that were infected. These investigators compared bone prosthesis interface activity to uri-

Figure 15 (A) Infected left hip replacement. There is increased activity along the bone prosthesis interface on the FDG image. The distribution of activity on the leukocyte/marrow study is spatially incongruent. A sinus tract can be seen on both the FDG and labeled leukocyte images. (B) Aseptically loosened left hip replacement. There is increased activity along the bone prosthesis interface on the FDG image, a finding that some investigators consider to be a very reliable indicator of infection. Inflammation can be present in aseptic loosening as well as in infection and it is not surprising that a non specific tracer like FDG cannot reliably differentiate between the two. The distribution of activity on the leukocyte/marrow study is spatially congruent, and the study is true negative. (Reprinted by permission of the Society of Nuclear Medicine from Love et al.⁵⁰)



nary bladder activity. Studies in which periprosthetic activity was intense were classified as positive for infection. Location of bone prosthesis interface activity was not analyzed. In contrast to previous investigations, they found that, although it was reasonably specific (81% for reader 1 and 85% for reader 2), the test was not sensitive for diagnosing infection (33% for reader 1, 56% for reader 2). The accuracy of the test, for both readers, was 69%, which was lower than the 80% accuracy of bone scintigraphy for both readers. False positive results were, not surprisingly, associated with foreign body reactions in aseptically loosened devices.

Love and coworkers⁵⁰ evaluated 59 failed lower-extremity joint replacements with coincidence detection FDG-PET and leukocyte/marrow imaging. These investigators used several different criteria for interpretation of the FDG images. The presence of bone prosthesis interface activity, with a target to background ratio greater than 3.6:1 for hip replacements and 3.1:1 for knee replacements were the most accurate criteria (71%) for diagnosing infection. The accuracy of leukocyte/marrow imaging, in their population, was 95%. These investigators found that regardless of the criteria used for interpretation, FDG does not differentiate infection from aseptic loosening and is not a suitable replacement for leukocyte/marrow imaging for diagnosing prosthetic joint infection (Fig. 15).

Summary

The primary role of nuclear medicine in the evaluation of the painful joint replacement is to differentiate aseptic loosening from infection. The relationship between aseptic loosening and inflammation renders nonspecific indicators of inflammation nearly useless. Although bone scintigraphy may be useful for screening purposes, combined leukocyte/marrow

scintigraphy, remains the procedure of choice for diagnosing infection. To replace leukocyte/marrow imaging, agents capable of differentiating infection from aseptic inflammation will need to be developed.

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