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# Nuclear Medicine and Infection Detection: The Relative Effectiveness of Imaging with $^{111}\text{In}$ -Oxine-, $^{99\text{m}}\text{Tc}$ -HMPAO-, and $^{99\text{m}}\text{Tc}$ -Stannous Fluoride Colloid-Labeled Leukocytes and with $^{67}\text{Ga}$ -Citrate\*

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With a current annual mortality rate of around 35% worldwide, infection remains a significant concern, and the diagnosis and localization of infectious foci is an important health issue. As an established infection-imaging modality, nuclear medicine plays a vital health-care role in the diagnosis and subsequent effective treatment of this condition. Despite the development of several newer radiopharmaceuticals,  $^{67}\text{Ga}$  and leukocyte imaging procedures have maintained their established place for infection. Several techniques in nuclear medicine significantly aid infection diagnosis, including imaging with  $^{111}\text{In}$ -oxine-,  $^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime-, and  $^{99\text{m}}\text{Tc}$ -stannous fluoride colloid-labeled leukocytes and with  $^{67}\text{Ga}$ -citrate. Each radiopharmaceutical has specific advantages and disadvantages that make it suitable to diagnose different infectious processes (e.g., soft-tissue sepsis, inflammatory bowel disease, osteomyelitis, occult fever, fever of unknown origin, and infections commonly found in immunocompromised patients). After finishing this article, the reader should be able to identify the properties of an ideal radiopharmaceutical for infection imaging, list a range of available infection-imaging radiopharmaceuticals, compare the relative results of a range of radiopharmaceuticals used internationally to detect infection in the body, understand several common infectious processes that can be diagnosed using nuclear medicine techniques, and select an appropriate radiopharmaceutical to image a range of infectious processes.

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Until recently, a clinician searching for the site of infectious foci using nuclear medicine had a choice between  $^{67}\text{Ga}$ -citrate imaging and  $^{111}\text{In}$ -oxine leukocyte imaging (1), but scientific advances (especially in nuclear medicine) have increased these choices considerably and continue to increase them. So in a world of new techniques such as antigranulocyte antibodies, radiolabeled nonspecific human IgG, interleukins, and antimicrobial peptides, is there any place for these dinosaurs of infection imaging (2)? The answer is a definite yes. Despite new developments and the proliferation of new antibiotics,  $^{67}\text{Ga}$ -citrate scintigraphy and leukocyte labeling are still widely used clinically because infection localization remains important for the clinical management of many patients (3).

Datz (4) gave a brief guideline regarding the properties of an ideal infection radiopharmaceutical: easy preparation, wide availability, low cost of both the pharmaceutical and the radionuclide, low toxicity, absence of an immune response to the compound, and high specificity. The radiopharmaceutical normally should not accumulate in blood, liver, spleen, gastrointestinal tract, bone, bone marrow, kidney, or muscle. Rapid washout from the background and target organ is also desirable. Rapid localization in infectious sites and the ability to differentiate bacterial infections from nonbacterial infections would be idyllic. Although no single current radiopharmaceutical fulfills all these requirements, the differences in the physiologic localization of each radiopharmaceutical are advantageous clinically (1).

This article identifies and compares the properties of several currently available infection-imaging agents and describes their usefulness in common infectious pathologies.

## INFECTION RADIOPHARMACEUTICALS

### <sup>111</sup>In-Oxine

Despite the development of other techniques, <sup>111</sup>In-oxine-labeled leukocytes remain the gold standard for intra-abdominal infection detection (5). During the cell-labeling process, <sup>111</sup>In-oxine diffuses into the cells and then separates from the lipophilic complex and binds irreversibly to the intracellular and nuclear components. The radionuclide then remains in the cell, undergoing natural decay (6).

<sup>111</sup>In-Oxine emits 2  $\gamma$ -rays, at 173 and 247 keV, and has a half-life of 67 h. Its long half-life and high in vivo stability allow the acquisition of late images, but its energy peaks are suboptimal (6) for acquisition using current  $\gamma$ -camera technology (7). Presently, the concentration that the radiolabel reaches in infectious foci is higher for <sup>111</sup>In-oxine imaging than for any other technique, but the harvesting and labeling procedures are time consuming and must be meticulously performed by experienced personnel (3).

In relation to Datz's requirements, <sup>111</sup>In-oxine leukocytes are quite difficult to prepare, and the radiolabel is often expensive and difficult to obtain (4). In vitro labeling of leukocytes opens the possibility of misadministration of blood (e.g., administration of HIV-infected blood) and is a biohazard to staff throughout the labeling process (4). Normal accumulation in the liver, bone marrow, and spleen is high. Maximal uptake is reached at 30 min (and remains until 24 h); this, combined with a low blood concentration and a blood half-clearance time of around 7.5 h, significantly decreases the imaging and diagnosis time (4).

The nonspecificity of leukocytes for infection (i.e., they can accumulate in sites of inflammation regardless of the presence of infection) is a disadvantage shared by virtually all infection-imaging agents. Leukocytes also do not generally detect viral and parasitic infections, limiting the utility of labeled leukocytes in some patient groups, such as those with AIDS (1).

<sup>111</sup>In-Oxine is preferred for the investigation of inflammation in the kidneys, bladder, and gallbladder and for chronic infection or occult fever. Sensitivity in the detection of osteomyelitis has been reported to vary from 50% to 90% (6).

<sup>111</sup>In-Oxine has several advantages, such as a normal biodistribution that is constant (in the liver, spleen, and bone marrow), compared with the drastic variations in normal biodistribution that can occur between individuals for <sup>67</sup>Ga-citrate. <sup>111</sup>In-Oxine normally does not accumulate in the genitourinary and gastrointestinal tracts, facilitating detection of infection in these areas. The results are usually available within 24 h, as opposed to 48 h or more for <sup>67</sup>Ga-citrate (8).

The most common indication for <sup>111</sup>In-oxine imaging is

chronic osteomyelitis, which includes infected joint prostheses, but its use in fever of unknown origin (FUO) and occult fever is more controversial (9).

### <sup>99m</sup>Tc-Hexamethylpropyleneamine Oxime (HMPAO)

During the binding process, the <sup>99m</sup>Tc-HMPAO complex enters the cell and then changes to a hydrophilic state and becomes trapped. Labeling is technically identical to <sup>111</sup>In-oxine labeling in that it requires separation of leukocytes, but not pure granulocytes, from the whole blood, followed by exposure to the complex. <sup>99m</sup>Tc-HMPAO particles are not stable in vivo and elute from cells at a rate of up to 7%/h. These secondary hydrophilic complexes are released into the blood and excreted through the kidneys and intestine. After labeling, a percentage of leukocytes is damaged, but not killed, by the cell irradiation resulting from internalization of the radionuclide-emitting low-energy electrons (0.4–17 keV) (9).

In view of the ideal requirements proposed by Datz (4), <sup>99m</sup>Tc-HMPAO can be seen to share many of the advantages and disadvantages of <sup>111</sup>In-oxine. Some exceptions are that the <sup>99m</sup>Tc label is cheaper and more readily available than the <sup>111</sup>In label; that <sup>99m</sup>Tc has a much higher photon flux, allowing improved visualization of areas such as feet; and that <sup>99m</sup>Tc-HMPAO localizes in infectious sites more rapidly than does <sup>111</sup>In-oxine. Decaying by the emission of 140-keV  $\gamma$ -rays, with a physical half-life of 6 h, <sup>99m</sup>Tc has optimal physical characteristics for  $\gamma$ -camera imaging, thus producing good-resolution images (6). The blood half-clearance time is 4 h (9), the sensitivity varies, and the target-to-background ratio for <sup>99m</sup>Tc is significantly lower than that for <sup>111</sup>In (1). <sup>99m</sup>Tc-HMPAO normally accumulates in the liver, spleen, bone marrow, kidneys, and gastrointestinal tract.

For the detection of lesions in the spleen, liver, and, to a lesser extent, lungs, <sup>99m</sup>Tc-HMPAO is suboptimal because of its biodistribution. However, uptake in inflamed bowel is typically well localized within 1 h after injection, before intestinal excretion begins, and can therefore be detected through imaging at that time. In pediatric patients and when better resolution is needed, such as for small-bowel involvement in Crohn's disease, <sup>99m</sup>Tc-HMPAO is preferred over <sup>111</sup>In-oxine because of superior resolution and count density (6).

The principal clinical indications for using <sup>99m</sup>Tc-HMPAO are irritable bowel disease (IBD), osteomyelitis, soft-tissue sepsis, and, to a lesser extent, occult fever. <sup>99m</sup>Tc-HMPAO imaging is usually indicated for acute soft-tissue and abdominal sepsis; communication between an abdominal abscess and bowel lumen may be difficult to demonstrate with this technique (9).

### <sup>99m</sup>Tc-Stannous Fluoride Colloid

When <sup>99m</sup>Tc-stannous fluoride colloid is used, leukocytes are labeled by phagocytosis (i.e., by the engulfment of the <sup>99m</sup>Tc-stannous fluoride colloid particle) (7).

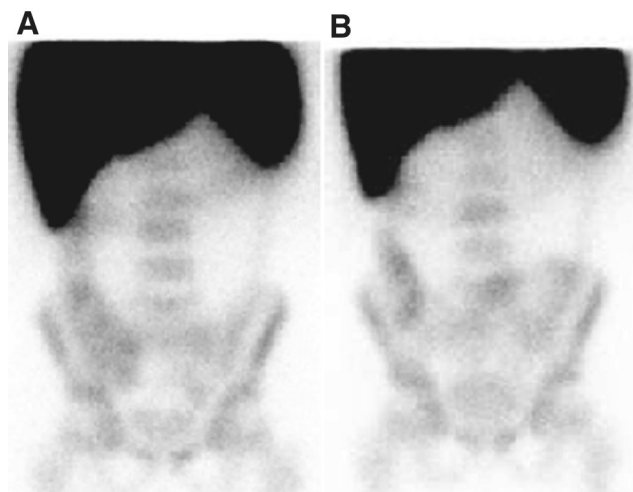
Colloid labeling of leukocytes offers a sensitive method

for the detection of infection, combined with the high image resolution and favorable radiation dosimetry characteristics offered by  $^{99m}\text{Tc}$ .  $^{99m}\text{Tc}$ -Stannous fluoride colloid is a relatively inexpensive, simple, non-labor-intensive procedure that uses whole blood (advantageous over other in vitro labeling methods) and, because available in kit form, is good for use in departments with limited leukocyte-labeling facilities (5,7). However, the colloid-labeling effectiveness is highly dependent on colloid size, for optimal phagocytosis by the leukocytes requires a range of 1–3  $\mu\text{m}$  (7).

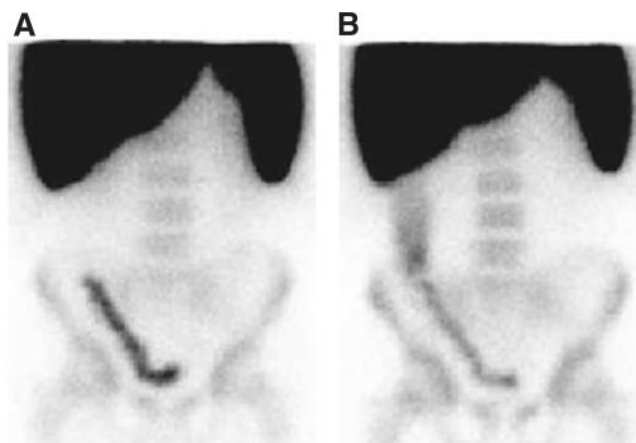
Compared with  $^{111}\text{In}$ -oxine,  $^{99m}\text{Tc}$ -stannous fluoride colloid demonstrates inferior sensitivity and specificity. For pathologies such as IBD and Crohn's disease, images at 1 and 3 h give a sensitivity of 76% (Figs. 1 and 2); the sensitivity and specificity increases to 86% and 95%, respectively, by including 24-h images in the analysis. However, because of the blood half-clearance time of  $^{99m}\text{Tc}$ -stannous fluoride colloid (1.2 h) and the physical half-life of  $^{99m}\text{Tc}$  (6 h), 24-h imaging with  $^{99m}\text{Tc}$  is not ideal. There is, however, a lack of solid documented clinical data determining the overall usefulness of this procedure, indicating an area for further investigation (7). In the United States,  $^{99m}\text{Tc}$ -stannous fluoride colloid-labeled leukocytes are not approved for clinical use; factors such as availability should always be considered when choosing a radiopharmaceutical.

#### $^{67}\text{Ga}$ -Citrate

The precise mechanism by which  $^{67}\text{Ga}$ -citrate accumulates in normal and pathologic tissues is not completely understood (8). It is widely accepted that  $^{67}\text{Ga}$ -citrate, as an analog of iron, binds in ionic form to circulating transferrin, uses transferrin receptors to access cells, and then becomes highly stable within cells (except red blood cells) (6,9). In acute inflammation,  $^{67}\text{Ga}$ -citrate is thought to leak through the vascular epithelium and bind to lactoferrin excreted in



**FIGURE 1.** Imaging of IBD (pancolitis) with  $^{99m}\text{Tc}$ -stannous fluoride colloid-labeled leukocytes. Image 1 h after injection (A), in conjunction with image 3 h after injection (B), shows clear segmental involvement.



**FIGURE 2.** Imaging of Crohn's disease with  $^{99m}\text{Tc}$ -stannous fluoride colloid-labeled leukocytes. Image 1 h after injection (A), in conjunction with image 3 h after injection (B), shows moderate to intense localization in large and small intestine.

loco by leukocytes or to siderophores produced by the infecting microorganisms themselves. Approximately 25% is excreted through the urinary system in the first 24 h, and excretion is then through the colon. About 75% of the injected dose is retained in the liver, bone, bone marrow, and soft tissues at 48 h (4,6).

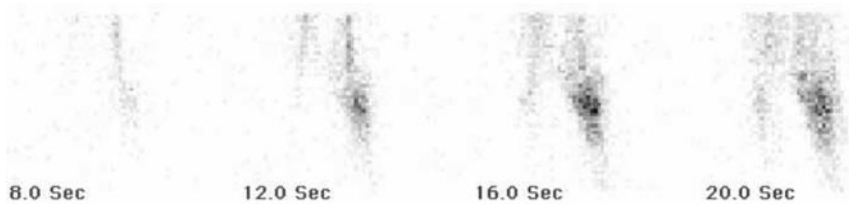
$^{67}\text{Ga}$ -Citrate successfully addresses many, but not all, of the criteria set out by Datz (4). It is easy to prepare and has low toxicity and a low target-to-background ratio.  $^{67}\text{Ga}$ -Citrate scanning has been described as outperforming most other techniques in detecting infection of both bacterial and nonbacterial origin, leading to its usefulness in immunosuppressed patients (1). Accumulation is normally present in liver, spleen, gastrointestinal tract, and kidneys but can vary significantly between individuals. Nonspecific uptake is also seen in several tumors. These variants often cause difficulty in the diagnostic process, and 24- to 72-h delayed images are therefore frequently required (1). With a physical half-life of 78 h and decay occurring through a broad range of  $\gamma$ -ray emissions,  $^{67}\text{Ga}$  has unfavorable physical characteristics for  $\gamma$ -camera imaging (6).

$^{67}\text{Ga}$ -Citrate imaging is an acceptable substitute when cell imaging is not possible, is an important infection localizer in its own right, and can be an important complement to leukocyte imaging (8). The use of  $^{67}\text{Ga}$ -citrate is generally limited to the study of chronic osteomyelitis, lung infections, and FUO, especially in immunocompromised patients. To increase its low specificity, it is often used in combination with other radiopharmaceuticals (6).

## PATHOLOGIES

### Soft-Tissue Sepsis

Producing excellent images of acute soft-tissue sepsis,  $^{99m}\text{Tc}$ -HMPAO is the preferred detection agent when sequential imaging at 1 and 4 h is used to delineate abdominal collections from nonspecific bowel activity. Whereas normal physiologic liver activity will decrease over time, in-



**FIGURE 3.** Anterior acquisition of sequential blood-flow images in  $^{99m}\text{Tc}$ -MDP study is important in diagnosis of osteomyelitis. Vascular activity is increased in left proximal tibia and knee.

trahepatic sepsis shows an area of increased uptake from 1 to 4 h. Nonspecific biliary excretion of  $^{99m}\text{Tc}$ -HMPAO may complicate the diagnosis of hepatobiliary sepsis;  $^{111}\text{In}$ -oxine, having no generalized biliary excretion, is therefore more effective for this pathology. For sepsis in and around the kidney, especially in patients with renal disease,  $^{111}\text{In}$ -oxine is again preferred, because of its lack of urinary excretion (9).

### Abscess

Abscess frequently occurs as a complication of surgery, infection, or inflammatory disease of the gastrointestinal tract (7). Abdominal abscesses in communication with bowel lumen are best identified with  $^{111}\text{In}$ -oxine, as  $^{99m}\text{Tc}$ -HMPAO will localize the abscess but may miss the communication because of nonspecific bowel activity (9).  $^{111}\text{In}$ -Oxine has no generalized bowel uptake and can show more than a third of all involved sites by 4 h after injection and more than 90% by 24 h (10). Subphrenic or subhepatic abscesses are ideally imaged using  $^{111}\text{In}$ -oxine, with imaging at 24 h, to distinguish normal liver and spleen activity from surrounding collections (9).

### Irritable Bowel Disease

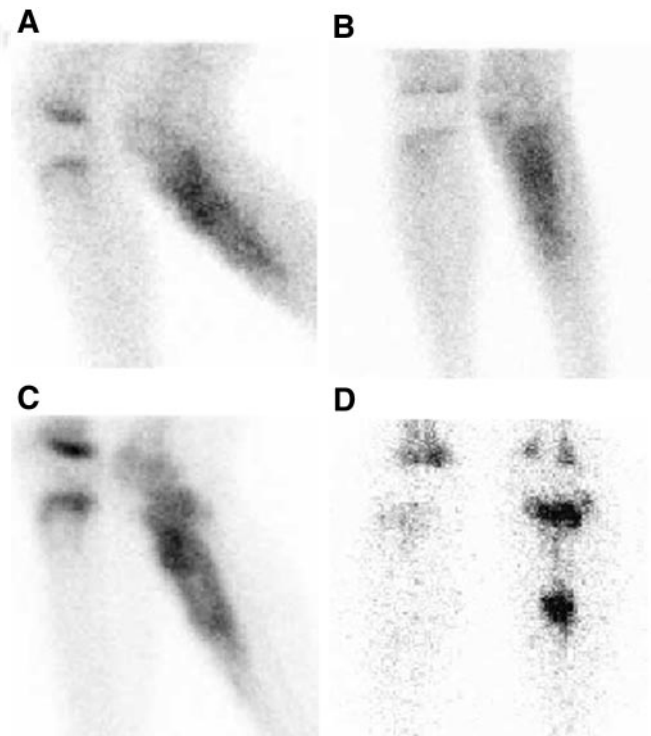
$^{99m}\text{Tc}$ -HMPAO has a major application in IBD through its superior ability to localize disease to specific bowel segments and reliably identify small-bowel disease (the shorter imaging time, compared with that of  $^{111}\text{In}$ -oxine, minimizes movement artifacts during such an acquisition). Sequential imaging is important and greatly affects the accuracy of this technique (9). Peters showed that an area of increased uptake at 1 and 4 h had a high predictive value (97% vs. endoscopy and 80% vs. histology) (9). An area of decreased (or no) uptake at 1 h and increased uptake at 4 h also had a positive predictive value (73% vs. endoscopy and 53% vs. histology) (9). Lack of an area of increased uptake at 1 and 4 h generally excludes any involvement (96% vs. endoscopy and 70% vs. histology) (9).

$^{111}\text{In}$ -Oxine scanning produces reliable images of the colon but has inferior image resolution that tends to miss disease in the small bowel because of the mobility and rapid transit of its contents. False-positive results caused by bowel uptake can result from recent surgery and gastrointestinal tract bleeding.  $^{99m}\text{Tc}$ -labeled leukocytes have the benefit of a lower radiation dose to the patient, and a diagnosis can often be determined from 1-h images rather than the 3-h images required of  $^{111}\text{In}$ -oxine imaging (Figs. 1 and 2) (9,10).

### Osteomyelitis

This condition can usually be diagnosed with 90% accuracy using a 3-phase  $^{99m}\text{Tc}$ -methylene diphosphonate (MDP) bone study but is nonspecific, as an increase in uptake identifies an area of increased bone-mineral turnover, not infection per se. For diagnosing osteomyelitis superimposed on noninfectious conditions that cause increased bone turnover and, thus, uptake, the technique is less successful (9).

$^{99m}\text{Tc}$ -HMPAO can be helpful for children younger than 6 mo, as at this age the sensitivity of  $^{99m}\text{Tc}$ -MDP is low (9).  $^{99m}\text{Tc}$ -HMPAO is generally more sensitive for the detection of acute osteomyelitis than of chronic osteomyelitis (with a high sensitivity [97.7%] and a specificity of 96.8%) (11).  $^{99m}\text{Tc}$ -HMPAO is also able to separate septic from aseptic bone lesions (Figs. 3 and 4) (11,12).



**FIGURE 4.** (A and B)  $^{99m}\text{Tc}$ -MDP blood-pool images of region of interest are important in diagnosis of osteomyelitis. (C) Delayed imaging of  $^{99m}\text{Tc}$ -MDP studies can give more detailed localization information concerning bone involved in infectious process. In addition to  $^{99m}\text{Tc}$ -MDP imaging, radiolabeled leukocytes can be used in diagnostic procedure when investigating osteomyelitis. (D) For this patient,  $^{99m}\text{Tc}$ -stannous fluoride colloid was administered 3 d after  $^{99m}\text{Tc}$ -MDP.  $^{99m}\text{Tc}$ -stannous fluoride colloid was imaged 3 h after injection.

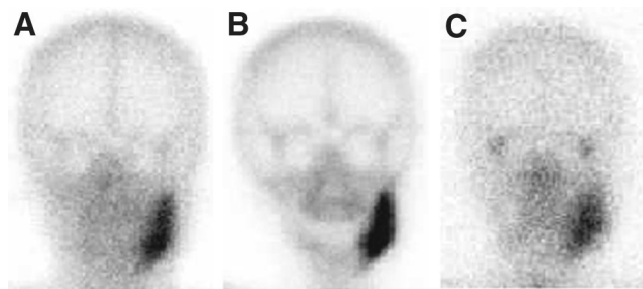
A  $^{67}\text{Ga}$ -citrate scan in conjunction with the  $^{99\text{m}}\text{Tc}$ -MDP bone scan can effectively detect infectious involvement. For vertebral osteomyelitis, leukocyte imaging is less than satisfactory, being neither sensitive nor specific because of normal bone marrow uptake in the axial skeleton (overall accuracy of 66%). However, Palestro quoted an accuracy of 86% for sequential  $^{99\text{m}}\text{Tc}$ -MDP/ $^{67}\text{Ga}$ -citrate imaging (8).  $^{67}\text{Ga}$ -Citrate is more suited to localizing a chronic infection than are  $^{99\text{m}}\text{Tc}$ -labeled leukocytes, which are better for acute inflammatory processes (Fig. 5) (9).

Leukocyte imaging can be applied to chronic osteomyelitis (including infected joint prostheses).  $^{111}\text{In}$ -Oxine is preferred over  $^{99\text{m}}\text{Tc}$ -HMPAO in such a case because it can be performed simultaneously with  $^{99\text{m}}\text{Tc}$ -stannous fluoride colloid scanning for the assessment of bone marrow involvement (mismatched defects identify infectious foci) (9,10). Infected orthopedic hardware will have increased uptake of  $^{111}\text{In}$ -oxine, whereas activity will be normal or decreased in healthy or loose prostheses (10).

Double labeling of leukocytes with  $^{99\text{m}}\text{Tc}$ -HMPAO and  $^{111}\text{In}$ -oxine is a technically simple, yet expensive, method in which 1-h  $^{99\text{m}}\text{Tc}$ -photopeak images of bone marrow are compared with 24-h  $^{111}\text{In}$ -photopeak images. In another simultaneous-acquisition method, involving  $^{111}\text{In}$ -oxine and  $^{99\text{m}}\text{Tc}$ -MDP ( $^{99\text{m}}\text{Tc}$ -MDP injected approximately 20 h after  $^{111}\text{In}$ -oxine injection), superimposed images clearly identify bone involved in infectious activity (9). For a more accurate diagnosis in difficult cases of osteomyelitis at sites with existing bone alteration or soft-tissue infection, combined radiopharmaceutical studies are usually preferred over simple leukocyte imaging (12).

### Occult Fever

Occult fever is defined as a fever for which investigation fails to establish a diagnosis or localize a pathology but strongly indicates a pyogenic cause, such as recent surgery, blood infection, endocarditis, and predisposing factors such as intravenous lines and peritoneal catheters (9). This indication is a well-recognized application for radiolabeled leukocytes, and according to Peters,  $^{111}\text{In}$ -oxine is best because of its localization process (9).



**FIGURE 5.**  $^{99\text{m}}\text{Tc}$ -MDP blood-pool phase (A) and delayed image (B) show abnormal uptake of tracer. (C)  $^{67}\text{Ga}$ -Citrate is used to ensure that increased bone activity is due to infection of bone—in this case, osteomyelitis.

### Fever of Unknown Origin

This fever is clinically defined as a body temperature exceeding  $38.3^{\circ}\text{C}$  for more than 3 wk, with the patient hospitalized for 1 wk while the fever is under investigation, and with no clue as to its cause (8). Peters stated that  $^{67}\text{Ga}$ -citrate is the best radiopharmaceutical for FUIO because of its ability to assess a wide spectrum of possible causes, including tumor or metastases, throughout the body. There is also a limited place for  $^{111}\text{In}$ -oxine in FUIO investigation, but no role has been established for  $^{99\text{m}}\text{Tc}$ -HMPAO (9). Even though a negative leukocyte scan (e.g.,  $^{111}\text{In}$ -oxine) can exclude an acute infection, it fails to identify the source of the FUIO. With only 25% of all FUIOs caused by infection, the ability of  $^{67}\text{Ga}$ -citrate to detect chronic infectious processes and neoplasms is highly desirable and compensates for its low specificity. Palestro (8) found that leukocyte labeling was most useful in patients symptomatic for less than 2 wk, and  $^{67}\text{Ga}$ -citrate has been found most useful for those symptomatic for more than 2 wk (9).

### Immunocompromised Patients

These patients have an increased susceptibility to numerous infections, often caused by organisms not typically pathogenic in an immunocompetent host (8). Despite the serious nature of these problems and the complications they can cause, patients often present with minimal signs and symptoms. The ability to rapidly perform whole-body surveys makes  $^{67}\text{Ga}$ -citrate a particularly attractive diagnostic tool for this population.

$^{67}\text{Ga}$ -Citrate scanning, in conjunction with chest radiography, is the procedure of choice for detecting the opportunistic respiratory infections and lymph node abnormalities that are so prevalent in this population. Leukocyte imaging is superior to  $^{67}\text{Ga}$ -citrate for the detection of sinusitis, bacterial pneumonia, and bowel infections (8). For pulmonary infection, negative  $^{67}\text{Ga}$ -citrate findings exclude infection with a high degree of certainty, and positive findings can be used in conjunction with other modalities to diagnose the specific pathologic process involved (13).

### CONCLUSION

Each of the radiopharmaceuticals detailed here, although not perfect, has an important role in the diagnosis of infection in varied situations. Clinical choices should not be limited to any single agent or any fixed combination; rather, practitioners should assess each case individually and choose the radiopharmaceutical that best suits the patient's situation and the purpose of the study (3).

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