resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

## PART VI: ISSUES REQUIRING FURTHER CLARIFICATION

A. Efficacy related to use of $^{111}$In leukocytes or $^{99m}$Tc leukocytes in many infections.
B. Minimum administered activity in children.

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# Procedure Guideline for Indium-111-Leukocyte Scintigraphy for Suspected Infection/Inflammation


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**Key Words:** practice guidelines; indium-111-leukocytes; inflammation/infection imaging

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## PART I: PURPOSE

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting and reporting the results of $^{111}$In-labeled leukocyte scintigraphy.

## PART II: BACKGROUND INFORMATION AND DEFINITIONS

Indium-111-leukocyte scintigraphy is a diagnostic imaging test which displays the distribution of radiolabeled leukocytes in the body. Regional, whole-body, planar and/or SPECT


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scintigrams of specific anatomic regions are obtained for suspected infection/inflammation.

In osteomyelitis, regional with $^{111}$In-leukocyte scintigraphy to detect sites of abnormal bone remodeling. Bone marrow scintigraphy using $^{99m}$Tc-sulfur colloid can be a useful adjunct to assess marrow distribution at suspected osteomyelitis sites, particularly when the site is adjacent to orthopedic prostheses. Gallium scintigraphy is usually preferred in patients with: neutropenia, fever of unknown origin, nonsuppurative or lymphocyte-mediated infections. Technetium-99m-HMPAO-labeled leukocyte scintigraphy is a frequently used option for acute infections, particularly in pediatric patients.

## PART III: COMMON INDICATIONS (*1–4*)

A. To detect sites of infection/inflammation in patients with granulocytosis and fever of unknown origin.
B. To localize an unknown source of sepsis and to detect additional site(s) of infection in patients with persistent or recurrent fever at known infection site.
C. To survey for site(s) of abscess or infection in a febrile postoperative patient without localizing signs or symptoms. Fluid collections, ileus, bowel gas and/or fluid, and healing wounds reduce the specificity of CT and ultrasound.
D. To detect site(s) and extent of inflammatory bowel disease (*3,5*).
E. To detect and follow-up osteomyelitis primarily when there is existing bone pathology such as infected joint prostheses, nonunited fractures or sites of metallic hardware from prior bone surgery (*6–8*).
F. To detect osteomyelitis in diabetic patients when degenerative or traumatic changes, neuropathic osteoarthropathy or prior osteomyelitis have caused increased bone remodeling (*8*).
G. To detect osteomyelitis involving the skull in postoperative patients and for follow-up of therapy (*9*).
H. To detect mycotic aneurysms, vascular graft and shunt infections (*10*).

## PART IV: PROCEDURE

A. Patient Preparation
Patients must be able to cooperate for whole-body or regional images which may require 30–60 min for completion. No special preparation for the test is needed.
B. Information Pertinent to Performing the Procedure
Coordination of this procedure with the referring physician is essential. Clinical history and the results of prior tests are helpful including: any history of surgery or trauma; the presence and location of surgical drains, skin or soft tissue infection and intravenous sites; and the presence of nasogastric and/or tracheostomy tubes. Bone radiographs and other imaging studies may be very helpful in assessing the cause of abnormal $^{111}$In-leukocyte localization in bone.
C. Precautions
Procedures and quality assurance for correct identification of patients and handling blood products are essential. The labeled leukocytes should be re-injected as soon as possible and preferably within 1–2 hr after labeling (*11*). Use of central intravenous lines requires strict sterile technique.
D. Radiopharmaceutical intravenous
1. Leukocytes are obtained from 40 to 80 ml of venous blood in adults. In children, the amount of blood depends on the patient size and circulating leukocyte count. The minimum volume of blood obtained is 10–15 ml. Circulating granulocyte counts should be a minimum of 1–3 $\times$ $10^3$ cells/ml. Whole blood is normally obtained by direct venipuncture and mixed immediately with ACD or heparin anticoagulant. Leukocytes are labeled with $^{111}$In-oxine by a variety of accepted methods (*2,3,12*).
2. Cell labeling should be performed by trained laboratory personnel and is performed in a laminar flow hood using sterile procedures. Care must be taken to *insure correct identification of patients and blood products*. All patients and laboratory procedures should have an appropriate quality control program.
3. The radiolabeled leukocytes are administered via intravenous injection. A large bore butterfly needle (18–20 g) is suggested. If an existing intravenous line is used for infusion, it should be flushed with normal saline before and after injection. Dextrose in water solutions should not be used, as these can cause clumping of labeled cells.
4. Radiolabeled leukocytes should be administered within 1–2 hr of cell labeling. Labeled cells stored longer than 3 hr have a significant loss of cell viability (*11*). Temperatures higher than 70°F tend to increase cell damage and should be avoided (*11*).
5. In adults, the administered activity is in the range of 10–20 MBq (0.3–0.5 mCi) (Table 1). Doses are

**TABLE 1**
Radiation Dosimetry for Adults

| Radiopharmaceuticals | Administered activity MBq (mCi) | Organ receiving largest radiation dose* mGy (rad) | Effective dose* mSv (rem) |
|---|---|---|---|
| $^{111}$In-leukocytes† | 10–18.5 i.v. (0.3–0.5) | 5.5 Spleen (20.4) | 0.590 (2.183) |
| $^{99m}$Tc-sulfur colloid‡ | 300–370 i.v. (8–10) | 0.077 Spleen (0.28) | 0.014 (0.052) |

*per MBq (per mCi).
†ICRP 53, normal liver, p. 256.
‡ICRP 53, normal liver, p. 180.

**TABLE 2**
Radiation Dosimetry for Children (5 yr old)

| Radiopharmaceuticals | Administered activity MBq/kg (mCi/kg) | Organ receiving largest radiation dose* mGy (rad) | Effective dose* mSv (rem) |
|---|---|---|---|
| $^{111}$In-leukocytes† | 0.15–0.25 i.v. (0.004–0.007) | 17 Spleen (63) | 1.8 (6.7) |
| $^{99m}$Tc-sulfur colloid‡ | 4.0–5.3 i.v. (0.10–0.15) | 0.25 Spleen (0.93) | 0.041 (0.15) |

*per MBq (per mCi).
†ICRP 53, normal liver, p. 256.
‡ICRP 53, normal liver, p. 180.

decreased in pediatric patients to 0.25–0.5 MBq/kg (7.5–15 μCi/kg) (Table 2). Minimum administered activity is 1.85–2.3 MBq (50–75 μCi) and maximum administered activity is 18.5 MBq (500 μCi).

6. In adults, the injected $^{99m}$Tc-sulfur colloid dose is in the range of 300–370 MBq (8–10 mCi) and 740–925 MBq (20–25 mCi) for $^{99m}$Tc-MDP.

E. Imaging Acquisition

1. Images are acquired at varying times depending on the clinical situation, usually 1–4 hr or 16–30 hr after injection. Images obtained after 16–24 hr postinjection may not contribute significant additional information, unless there is too much residual blood-pool activity on the early scintigrams. Planar images are usually acquired for 10–15 min. Imaging times of 15–20 min or longer may be needed in low count regions (e.g., distal limb in osteomyelitis).
2. Planar images are usually obtained using a large field of view gamma camera fitted with a medium-energy collimator. Energy windows of 15%–20% are centered over the 173- and 247-keV $^{111}$In photopeaks.
3. Whole-body scans are acquired using single or dual large field of view detector(s). Scanning times vary with the type of equipment but are generally 25–35 min (rate of 5–6 cm/min).
4. Technetium-99m-sulfur colloid imaging is usually done after $^{111}$In-leukocyte imaging if there is a question concerning bone marrow distribution. Imaging is delayed 30 min postinjection to allow sufficient time for satisfactory clearance of blood-pool activity.
   a. Planar images of involved sites are obtained to assess pattern of bone marrow uptake.
   b. Corresponding views of contralateral regions are useful for comparison.
   c. A gamma camera fitted with a medium-energy collimator and a 15%–20% energy window over the $^{99m}$Tc photopeak are used.
   d. Ten-minute regional views are usually satisfactory (counts will vary depending on the region of interest).
   e. Image intensity is adjusted to provide images comparable to $^{111}$In-leukocyte images to facilitate comparison of relative uptake at sites of suspected infection.
   f. Combined $^{99m}$Tc-sulfur colloid/$^{111}$In-leukocyte scans can be obtained with additional views in difficult cases.
5. Simultaneous $^{111}$In-leukocyte/$^{99m}$Tc-MDP bone images can be obtained using a gamma camera that can acquire and discriminate the 140-keV $^{99m}$Tc photons from the $^{111}$In photons. Each $^{111}$In-leukocyte/$^{99m}$Tc bone image is acquired using a medium-energy collimator for 50K counts in the $^{111}$In window or for 15 min, 4 hr and/or 16–30 hr after injection of the $^{111}$In-leukocytes.
   a. A 15% window at the 140-keV $^{99m}$Tc peak and a 15% window at the 247-keV $^{111}$In photopeaks is used if the $^{99m}$Tc dose is injected on Day 1 prior to $^{111}$In-leukocyte imaging. Many centers also use a 10% or 15% window at the 173-keV $^{111}$In photopeak for delayed $^{111}$In-leukocyte images obtained on Day 2 (18–30 hr) after the $^{99m}$Tc dose has been injected.
   b. Combined images can also be obtained with older cameras that can only acquire one radioisotope at a time. A 10% window at the 140-keV $^{99m}$Tc peak is used for a 5-min or 400K bone image. Without moving the patient or camera, the window is changed to a 15%–20% window at the 247-keV $^{111}$In peak and a 50K count or 15-min $^{111}$In-leukocyte image is acquired.
6. For the axial skeleton, simultaneous $^{111}$In-leukocyte/$^{99m}$Tc-sulfur colloid or $^{111}$In-leukocyte/$^{99m}$Tc-MDP SPECT imaging can be obtained of the axial skeleton to better assess the extent of bone or bone marrow involvement, and to help differentiate soft-tissue from bone uptake.
   a. Indium-111-leukocyte/bone SPECT scans are best obtained using dual- or triple-detector systems equipped with medium-energy collimators. The images are acquired in dual-isotope mode using the window settings as described in section IV.E.5.a.
   b. For three-detector systems, projection images from the $^{99m}$Tc and $^{111}$In energy windows are obtained over 20–30 min (See Society of Nuclear Medicine Procedure Guideline for General Imaging).

F. Interventions

In patients with suspected infected joint prosthesis, aspiration of the involved joint should be avoided during the interval between injection and imaging to avoid bleeding and removal of localized $^{111}$In-leukocyte activity.

G. Processing

See Society of Nuclear Medicine Procedure Guideline for General Imaging for details.

H. Interpretation/Reporting

1. Normal Findings (*1,3,4*)
   Indium-111-leukocyte distribution at 18–24 hr is primarily confined to the reticuloendothelial system of the liver, spleen, bone marrow and major blood vessels. No bowel or bladder activity is present.
2. Inflammatory Bowel Disease (*3,5*)
   a. Images obtained 0.5–1 hr and 2–3 hr after injection are helpful to assess site(s) and extent of bowel involvement.
   b. Inflammatory bowel disease shows early regional or diffuse bowel localization with progression of activity along the bowel lumen over time due to $^{111}$In-leukocyte transudation. There is good correlation with site and inflammation activity index.
3. Abscess Detection
   One-third to one-half of sites are visualized by 4 hr postinjection and more than 90% of sites by 24 hr. Uptake is usually equal to or greater than liver activity (*4*).
4. Osteomyelitis (*7,8*)
   Focal $^{111}$In-leukocyte accumulation that is greater than adjacent or contralateral background activity and corresponds to a bone site, or more specifically to a site of increased bone radiopharmaceutical accumulation (but does not have to be of the same intensity).
   a. In the presence of orthopedic hardware or prostheses, normal bone marrow is disrupted and displaced, making interpretations difficult in these regions. Comparison of $^{111}$In-leukocyte localization with $^{99m}$Tc-sulfur colloid uptake using combined or sequential $^{111}$In-leukocyte/$^{99m}$Tc-colloid

images is usually necessary. Comparison with adjacent or contralateral regions can also be helpful.

b. Indium-111-leukocyte uptake is typically increased in the vicinity of infected orthopedic hardware, and normal or decreased (due to displaced marrow) in the presence of normal or loose, but noninfected prostheses. Infection is likely when there is abnormal $^{111}$In-leukocyte localization greater than the $^{99m}$Tc-sulfur colloid bone marrow activity (discordant activity).

c. Comparison with radiographs is often very helpful.

d. For SPECT images, a diagnosis of osteomyelitis is indicated when abnormal focal $^{111}$In-leukocyte localization corresponds to abnormal bone uptake on two or more adjacent 6–8-mm tomographic slices and is identified in at least one plane. Soft-tissue infection is likely if $^{111}$In-leukocyte localization does not correspond to abnormal bone tracer uptake.

I. Quality Control

1. The labeling efficiency of $^{111}$In-leukocytes may be determined by recentrifugation (approximately 150 g for 8 min) of the labeled leukocytes once they have been washed and resuspended in 5 ml of buffered saline. The supernatant is poured into a separate counting tube and the leukocyte pellet is resuspended in 5 ml of cell-free plasma. Each tube is then counted in a dose calibrator. Labeling efficiency = (resuspended In-leukocyte activity)/(resuspended In-leukocyte activity) + (supernatant activity).
2. Leukocyte clumping may be checked by looking at a drop of $^{111}$In-leukocyte suspension placed on a hemocytometer slide and viewed under a microscope under low- and medium-power. There should be very little clumping present.
3. A rough estimate of the number of cells labeled can be made by visual examination of a representative sample on a hemocytometer slide. The average number of cells per 50 micron (small) square is then determined. The number of cells/cm$^3$ (ml) = the average number of cells/small square × 2,000,000.

J. Sources of Error (*3,4*)

1. Potential causes for focal $^{111}$In-leukocyte soft-tissue localization other than infection:
   Intravenous line localization, accessory spleen, acute bleeds, hematomas, inflammatory response to foreign body, neoplasm, localized bile collections, bowel inflammation, endometritis, vaginitis, myositis ossificans, bladder catheters, nasogastric and tracheostomy tubes and recent infarcts. Rare cases of false-positive $^{111}$In-leukocyte scans caused by increased numbers of labeled platelets have been reported.
2. Potential causes of false-negative $^{111}$In-leukocyte studies:
   Chronic abscess more than 3 wk of age, lymphocytic mediated infection (tuberculosis, granulomatous process, viral infection, etc.), hepatic or splenic abscesses, abscess adjacent to the liver or spleen, or low-grade or chronic osteomyelitis.
3. Bowel $^{111}$In-leukocyte localization not caused by infection:
   Irritative bowel lesion(s) such as stomas or from multiple enemas, gastrointestinal bleeding or infarction, fistula to bowel from an adjacent abscess, or swallowed labeled cells (bronchitis, sinusitis, pneumonia).
4. Noninfectious causes of $^{111}$In-leukocyte bone localization:
   Active rheumatoid or traumatic/degenerative arthritis, acute fractures (less than 2 mo), traumatic or neuropathic arthropathy, acute bone infarcts, or a foreign body reaction. Rarely neoplasms such as lymphoma, adjacent soft-tissue inflammation such as myositis or active heterotopic bone formation can cause $^{111}$In-leukocyte uptake.
5. Errors in interpretation in suspected osteomyelitis cases can be minimized by obtaining $^{99m}$Tc-sulfur colloid marrow studies in cases where $^{111}$In-leukocyte images are indeterminate (neither clearly positive or negative).
   a. Concordant $^{111}$In-leukocyte and $^{99m}$Tc-sulfur colloid marrow uptake is normal, whereas a discordant pattern, with $^{111}$In-leukocyte uptake greater in extent and/or intensity compared to marrow uptake, is highly suspicious for infection.
   b. Simultaneous acquisition of $^{111}$In-leukocyte/$^{99m}$Tc-MDP bone images helps distinguish adjacent soft-tissue infection from bone infection increasing the specificity for osteomyelitis.
6. Extensive soft tissue surrounding bone may give the appearance of underlying bone involvement. (In this circumstance SPECT may be helpful.)
7. If a 20–30-mCi dose of $^{99m}$Tc bone tracer is injected on the same day as the $^{111}$In-leukocyte images, the intense $^{99m}$Tc activity can produce photon overload in the lower $^{111}$In window, which may cause a corresponding false-positive focus (*11*). Use of the lower $^{111}$In window should be *avoided* if $^{99m}$Tc bone tracer is injected just prior to $^{111}$In-leukocyte imaging. Similarly, on the delayed images intense $^{111}$In activity may scatter into the $^{99m}$Tc window. The contribution that scatter makes to the final image varies from camera to camera and should be evaluated.
8. False-positive scan interpretations can occur in patients with very active soft-tissue infection adjacent to a thin and/or relatively vascular bone such as the maxilla, mandible or pelvis.
9. Causes for abnormally decreased $^{111}$In-leukocyte accumulation (*3*):
   a. Osteomyelitis of the spine will often appear as focal decreased uptake compared to adjacent bone marrow.
   b. False-negative scans for detection of osteomyelitis can occur when the patient is imaged after being on intravenous antibiotics for several weeks. If intravenous antibiotics have been stopped for 2–4 wk prior to imaging, a false-negative scan is not likely to occur.

## PART V: DISCLAIMER

The Society of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different than the spectrum of patients seen in a more general practice setting. The

appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

## PART VI: ISSUES REQUIRING FURTHER CLARIFICATION

A. Relative efficacy of gallium, $^{99m}$Tc-leukocyte and $^{111}$In-leukocyte scintigraphy in different clinical settings.
B. Better definition of the role of $^{99m}$Tc bone marrow scintigraphy.

## PART VII: CONCISE BIBLIOGRAPHY


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