Procedure Guideline for Technetium-99m-HMPAO-Labeled Leukocyte Scintigraphy for Suspected Infection/Inflammation

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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 ^{99m}Tc-HMPAO-labeled leukocyte (^{99m}Tc-leukocyte) scintigraphy.

PART II: BACKGROUND INFORMATION AND DEFINITIONS

Technetium-99m-leukocyte scintigraphy consists of regional, whole-body, planar and SPECT scintigrams obtained after intravenous injection of ^{99m}Tc-labeled leukocytes.

PART III: COMMON INDICATIONS *(1–3)*

A. To detect suspected sites of *acute* inflammation/infection in the febrile patient with or without localizing signs or symptoms.
   1. To detect site(s) of inflammation as cause of abdominal pain.
   2. To localize site(s) of infection in patients with granulocytosis and/or positive blood cultures.

B. To detect and determine the extent of inflammatory or ischemic bowel disease—may be more sensitive than ^{111}In-leukocyte scintigraphy for detection of disease, particularly involving the small bowel (*4*). Indium-111-leukocytes are preferred for quantitative assessment (*5*).

C. To detect and assess (follow-up) musculoskeletal infection such as septic arthritis and osteomyelitis.
   1. May be more sensitive for detection of acute compared to chronic osteomyelitis.
   2. Combined ^{111}In-white blood cell (WBC)/^{99m}Tc-MDP bone and/or ^{111}In WBC/^{99m}Tc-sulfur colloid marrow scans may be preferred in difficult cases of osteomyelitis at sites with existing bone alteration and/or adjacent soft-tissue infection instead of ^{99m}Tc-WBC imaging.

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PART IV: PROCEDURE

A. Patient Preparation

In children, a 2–4-hr fast may help reduce hepatobiliary excretion and bowel transit. In adults, fasting may have less effect.

B. Information Pertinent to Performing the Procedure
   1. Coordination of this procedure with the referring physician is essential. Clinical history and the results of prior tests are essential 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, bone scans and other imaging studies may be very helpful in assessing the cause of abnormal ^{99m}Tc-leukocyte localization in bone.
   2. Technetium-99m-labeled compared to ^{111}In-labeled leukocyte scintigraphy has the advantages of earlier and shorter imaging times, lower absorbed radiation dose and a smaller blood sample for labeling leukocytes.
   3. Indium-111-leukocyte scintigraphy may be preferred in some patients with suspected sites of inflammation or infection in the abdomen/pelvis, since unlike ^{99m}Tc-leukocytes, there is normally no excretion into gastrointestinal or urinary tracts.
   4. Indium-111-leukocyte scintigraphy may be preferred in patients with suspected sites of infection in the chest who might have prolonged lung blood-pool activity due to congestive heart failure, septic shock or renal failure, etc. (see the Society of Nuclear Medicine Procedure Guideline for Indium-111-Leukocyte Scintigraphy for Suspected Infection/Inflammation).
   5. Gallium-67 is preferred for evaluation and follow-up of active lymphocytic or granulomatous inflammatory processes such as tuberculosis or sarcoidosis especially in the immunocompromised patient.

C. Precautions
   1. Procedures and quality assurance that insure correct identification of patients and their blood samples throughout the entire labeling procedure are essential. The same precautions should be taken as for blood transfusions.

2. The labeled cells should be reinjected as soon as possible within 1.5–2 hr and no later than 3–4 hr after obtaining the blood sample (*6*).
3. Use of a central intravenous line requires strict sterile technique.
4. It is mandatory that the OSHA Guideline for safe handling of human blood products be followed at all times.

D. Radiopharmaceutical
For additional details on labeling, see Society of Nuclear Medicine Procedure Guideline for Imaging with Radiopharmaceuticals.
1. Leukocytes are obtained from 20–40 ml of venous blood in adults. Circulating granulocyte counts should be a minimum of 2×10^9 cells/liter. Whole blood is normally obtained by direct venipuncture and mixed immediately with ACD anticoagulant.
2. In children, the amount of blood depends on the patient size and circulating leukocyte count. The minimum volume of blood obtained is about 10–15 ml.
3. Only the unstabilized form of exametazime (HMPAO) should be used for labeling (do not use methylene blue in this procedure). For details of cell labeling, see articles in bibliography (*7–9*).
4. For adults, the usual administered activity is 185–370 MBq (5–10 mCi) of ^{99m}Tc-HMPAO-labeled WBCs (Table 1).
5. For children, the usual administered activity is 3.7–7.4 MBq/kg (0.1–0.2 mCi/kg). The usual minimum pediatric administered activity is 18–37 MBq (0.5–1.0 mCi) (Table 2). The maximum administered activity in a child should not exceed the maximum administered activity for an adult.
6. Exametazime (HMPAO) is a lipophilic complex which penetrates the leukocyte cell membrane and is retained within the cell.

TABLE 1
Radiation Dosimetry for Adults

Radiopharmaceutical	Administered activity MBq (mCi)	Organ receiving the largest radiation dose*† mGy (rad)	Effective dose*† mSv (rem)
^{99m}Tc-HMPAO-leukocytes	185–370 i.v. (5–10)	0.15 Spleen (0.56)	0.017 (0.063)

*ICRP 53, p. 232.
†per MBq (per mCi).

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

Radiopharmaceutical	Administered activity MBq/kg (mCi/kg)	Organ receiving the largest radiation dose*† mGy (rad)	Effective dose*† mSv (rem)
^{99m}Tc-HMPAO-leukocytes	2.50–5.0 i.v. (0.07–0.14)	0.48 Spleen (1.8)	0.054 (0.20)

*ICRP 53, p. 232.
†per MBq (per mCi).

TABLE 3

Diagnosis	Early imaging	Delayed imaging	16–24 hr imaging
Abdominal abscess	0.5–1 hr for adults 20–40 min for children	Sequential to 4 hr	Rarely, if early images are negative, but requires longer imaging times.
Inflammatory or ischemic bowel disease	0.5–1 hr for adults 20–40 min for children	Sequential up to 4 hr, physiologic bowel activity may interfere on later images.	Usually not indicated since physiologic bowel activity is present.
Chest-pulmonary infection	Physiologic lung activity may interfere.	4–8 hr	If early images are negative, requires longer imaging times.
Osteomyelitis	May not have sufficient localization.	4–8 hr	If early images are negative or equivocal (requires longer imaging times).

7. The spleen, bladder and large bowel receive the largest absorbed radiation dose.
8. Leukocyte migration, chemotaxis, phagocytosis, intracellular killing, adhesive and superoxide generation have been shown to remain normal after labeling with ^{99m}Tc- HMPAO (*2*).

E. Image Acquisition (Table 3)
1. A large field of view gamma camera with a low-energy, high-resolution collimator is usually preferred. If count rates are poor on the 16–24 hr delayed images, a LEAP collimator can be used. The pulse-height analyzer is centered at 140 keV using a 15%–20% window.
2. Early imaging of the pelvis and abdomen is *essential* (bowel activity is seen in 20%–30% of children by 1 hr and 2%–6% of adults by 3–4 hr postinjection).
   a. Regional images are obtained for at least 800,000 counts/large field of view of 5–10 min/view.
   b. Whole-body images should include the anterior and posterior head, chest, abdomen, pelvis and extremities when clinically indicated. A limited study to evaluate a particular region of the body is acceptable in select cases.
3. Images of the limbs should be acquired for 10 min/view at 4–8 hr and at least 15 min/view at 16–24 hr (particularly for osteomyelitis).
4. SPECT images of the chest, abdomen/pelvis or spine may be helpful.

F. Interventions
None.

G. Processing
See the Society of Nuclear Medicine Procedure Guideline for General Imaging.

H. Interpretation/Reporting (*1–3*)
1. Normal Findings
   a. The blood clearance half-life of ^{99m}Tc-leukocytes is about 4 hr, and activity may be seen in the heart, lungs and great vessels, including the ileofemoral vessels even on delayed images (greater than 4 hr)

due to slow clearance. Indium-111-leukocytes may be preferred for detection of vascular graft or dialysis shunt infection, since blood-pool activity is much lower relative to sites of abnormal localization (especially on 18–24-hr delayed images).

b. Bowel activity secondary to hepatobiliary secretion of ^{99m}Tc hydrophilic complexes is seen in 20%–30% of children by 1 hr, but is usually not seen in adults prior to 4 hr. In adults, physiologic bowel activity is usually faint if seen at 4 hr and is usually seen in the terminal ileum or right colon, increasing over time.

c. Renal and bladder activity is seen by 15–30 min in all patients with normal renal function. The patient should try to empty his/her bladder prior to pelvic imaging.

d. Uniform physiologic gallbladder activity can be seen in 4% of patients by 2–4 hr and up to 10% of patients by 24 hr. A curvilinear pattern at the margin is suspicious for inflammation of the gallbladder wall.

e. The spleen, liver, bone marrow, kidneys, bowel, bladder and major blood vessels will normally be visualized.

2. Abnormal Findings

a. Abnormal bowel localization may be seen by 15–30 min and usually increases in intensity over the next 2–3 hr.

1. The degree and extent of bowel disease is usually demonstrated by 1–2 hr.
2. Shifting patterns of bowel activity on later images usually indicates distal transit of labeled granulocytes, or at times, bleeding within the bowel lumen.

b. Lung activity is *mostly* cleared by 1–4 hr, unless there is pulmonary edema, diffuse inflammatory lung disease, atelectasis, renal failure or adult respiratory distress syndrome.

c. Focal abdominal activity outside the liver and bowel is likely to indicate infection/inflammation but can vary greatly in intensity depending on the degree of inflammation. Caution should be used in interpretation of a focal site of abnormal localization as indicating a drainable abscess and correlation with other imaging modalities is recommended.

d. Infection involving the spine may present as areas of *increased or decreased* activity compared to normal bone marrow localization. Photopenic or "cold" defects may be due to osteomyelitis, but other causes such as compression fracture, neoplasm, postirradiation changes, postsurgical or anatomic deformities should also be considered. Comparison to ^{99m}Tc sulfur colloid imaging is suggested.

I. Quality Control

1. The labeling efficiency of ^{99m}Tc-labeled leukocytes may be determined by recentrifugation (approximately 150 g for 8 min) of the labeled leukocytes. 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 Tc-leukocyte activity)/(resuspended Tc-leukocyte activity) + (supernatant activity).
2. Leukocyte clumping is checked by looking at a drop of ^{99m}Tc-labeled leukocyte suspension placed on a hemacytometer slide and viewed under a microscope under low- and medium-power. There should be no clumping. The leukocyte suspension can be filtered with a 16-g filter needle to remove leukocyte clumps.
3. A rough estimate of the number of cells labeled can be made by visual examination of a representative sample on a hemacytometer 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. This step is optional.

J. Sources of Error

1. Note that the normal biodistribution of ^{99m}Tc-leukocytes differs from ^{111}In-leukocytes. In adults, a changing pattern of bowel activity prior to 4 hr is likely from intraluminal transit of labeled cells secondary to inflammatory bowel disease, bleeding or may indicate a fistula from an abscess. In children, progressive physiologic bowel activity can be present by 1 hr. Delayed imaging alone is often misleading in inflammatory bowel disease. Bone marrow expansion or hyperplasia can alter the normal marrow patterns. (See Society of Nuclear Medicine Procedure Guideline for Indium-111-Leukocyte Scintigraphy for Suspected Infection/Inflammation, section IV.J. for other sources of errors.)
2. False-negative results occur due to rapid bowel clearance of labeled leukocytes from inflamed bowel, particularly in the small bowel. Bladder activity may mask a pelvic site of infection (voiding, or when necessary, catheterization is suggested prior to pelvic imaging). Normal renal activity can make it difficult to detect pyelonephritis and/or a small renal abscess. Chronic walled off abscesses or low grade infections, particularly in bone have less ^{99m}Tc granulocyte accumulation and are more likely not to be visualized. Residual diffuse lung activity, particularly in patients with heart or renal failure, may obscure focal lung infections even as late as 4–6 hr postinjection.
3. False-positive results can occur from rapid small bowel transit of hepatobiliary secretion and focal accumulation of activity in the cecum, particularly if imaging is done after 1 hr in children and 4 hr in adults. Active gastrointestinal bleeding or swallowed cells can be mistaken for an inflammatory bowel process. Focal collections of inflamed peritoneal fluid, or sites of focal bowel inflammation can be mistaken for abscess. Hematomas and inflammation around neoplasms such as lymphomas may also mimic an abscess. Noninfected vascular grafts and/or shunts can show increased localization due to bleeding or non-infected reparative process.

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 ^{111}In-labeled leukocytes and ^{99m}Tc-labeled leukocytes in different clinical conditions.
B. Radiation effects using ^{99m}Tc doses greater than 20 mCi on granulocyte viability during ^{99m}Tc-HMPAO labeling procedure.

PART VII: CONCISE BIBLIOGRAPHY

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PART VIII: LAST HOUSE OF DELEGATES APPROVAL DATE

January 14, 1996

PART IX: NEXT ANTICIPATED APPROVAL DATE

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Procedure Guideline for Gallium Scintigraphy in the Evaluation of Malignant Disease

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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 ^{67}Ga-citrate imaging in the evaluation of patients with malignant disease.