Society of Nuclear Medicine Procedure Guideline for ^{99m}Tc-Exametazime (HMPAO)-Labeled Leukocyte Scintigraphy for Suspected Infection/Inflammation

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I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of ^{99m}Tc-exametazime (HMPAO) labeled leukocyte (^{99m}Tc-leukocyte) scintigraphy.

II. Background Information and Definitions

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

III. Examples of Clinical or Research Applications for ^{99m}Tc-Leukocyte Scintigraphy

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 a 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. This technique may be more sensitive than ^{111}In-leukocyte scintigraphy for detection of disease, particularly involving the small bowel. ^{111}In-leukocytes are preferred for quantitative assessment.

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

IV. Procedure

A. Patient Preparation

In children, a 2–4 h 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 administration sites and the presence of nasogastric and/or ostomy (tracheostomy, colostomy, feeding gastrostomy, etc.) 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. ^{99m}Tc-labeled leukocyte scintigraphy, when compared with ^{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. ^{111}In-leukocyte scintigraphy is preferred in some patients with suspected sites of inflammation or infection in the abdomen/pelvis, because, unlike ^{99m}Tc-leukocytes, there is normally no excretion into gastrointestinal or urinary tracts.
4. ^{111}In-leukocyte scintigraphy may be preferred in patients with suspected sites of infection in the chest who might have prolonged lung blood pool activity as a result of congestive heart failure, septic shock, renal failure, etc. (See the Society of Nuclear Medicine Procedure Guideline for ^{111}In-Leukocyte Scintigraphy for Suspected Infection/Inflammation.)
5. ^{67} Ga is preferred for evaluation and follow-up of active lymphocytic or granulomatous inflammatory processes, such as tuberculosis or sarcoidosis, and especially in the immunocompromised patient for detecting opportunistic infections.

C. Precautions

Procedures and quality assurance measures 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 h after labeling. Use of central intravenous lines requires strict sterile technique.

D. Radiopharmaceutical

(For additional details on labeling see Society of Nuclear Medicine Procedure Guideline for Use of Radiopharmaceuticals.)

1. Leukocytes are obtained from 40–60 mL of venous blood in adults. Circulating granulocyte counts should be a minimum of 2×10^6 cells/mL. 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.
4. For adults, the usual administered activity is 185–370 MBq (5–10 mCi) of ^{99m}Tc-HMPAO-labeled WBC.
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). 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.
7. The spleen, bladder, and large bowel receive the largest radiation absorbed dose.
8. Leukocyte migration, chemotaxis, phagocytosis, intracellular killing, and adhesive and superoxide generation have been shown to remain normal after labeling with ^{99m}Tc-HMPAO.

E. Image Acquisition

1. A large-field-of-view gamma camera with a low-energy high-resolution collimator is usually preferred. If count rates are low on the 16–24-h delayed images, a low-energy all-purpose 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 h and 2%–6% of adults by 3–4 h after injection). See normal findings in section IV.H.1.b.
   a. Regional images are obtained for at least 800,000 counts/large field of view or 5–10 min/view.

Radiation Dosimetry: Adults[1]

Radiopharmaceuticals	Administered activity MBq (mCi)	Organ receiving the largest radiation dose mGy/MBq (rad/mCi)	Effective dose equivalent mSv/MBq (rem/mCi)
^{99m}Tc-exametazime (HMPAO) leukocytes [1]	185–370 iv (5–10)	0.15 Spleen (0.56)	0.017 (0.063)

[1] International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. London, UK: ICRP; 1988:232.

Radiation Dosimetry: Children (5 Years Old)

Radiopharmaceuticals	Administered activity MBq/kg (mCi/kg)	Organ receiving the largest radiation dose mGy/MBq (rad/mCi)	Effective dose equivalent mSv/MBq (rem/mCi)
^{99m}Tc-exametazime (HMPAO) leukocytes [1]	3.7–7.4 iv (0.1–0.2)	0.48 Spleen (1.8)	0.054 (0.20)

[1] International Commission on Radiological Protection. *Radiation Dose to Patients from Radiopharmaceuticals.* ICRP Publication 53. London, UK: ICRP; 1988:232.

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 specific region of the body is acceptable in select cases.

3. Images of the limbs should be acquired for 10 min/view at 4–8 h and at least 15 min/view at 16–24 h (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 Criteria

Accurate interpretation of labeled leukocyte scintigraphy requires knowledge of the normal and abnormal variants of leukocyte localization.

1. Normal Findings
   a. The blood clearance half-life of ^{99m}Tc-leukocytes is about 4 h, and delayed images (longer than 4 h) may be preferred for detection of vascular graft or dialysis shunt infection. ^{111}In-leukocytes may be preferred for detection of vascular graft or dialysis shunt infection, because blood pool activity is much lower relative to sites of abnormal localization (especially on 18–24-h delayed images).
   b. Bowel activity secondary to secretion of ^{99m}Tc complexes is seen in 20%–30% of children by 1 h but is usually not seen in adults before 4 h. In adults, physiologic bowel activity is usually faint if seen at 4 h 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 before pelvic imaging.
   d. Uniform physiologic gallbladder activity can be seen in 4% of patients by 2–4-h and up to 10% of patients by 24 h. A curvilin-

ear pattern at the margin is suspicious for inflammation of the gallbladder wall.

Image Acquisition

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

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 h.
      i. The degree and extent of bowel disease is usually demonstrated by 1–2 h.
      ii. 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 usually clears by 4 h, unless there is pulmonary edema, diffuse inflammatory lung disease, atelectasis, renal failure, sepsis, 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 with normal bone marrow localization. Photopenic or "cold" defects may indicate osteomyelitis, but other causes, such as compression fracture, neoplasm, postirradiation changes, or postsurgical or anatomic deformities, should also be considered.

I. Reporting

The report should include the following information:

1. Indication for the study
2. Procedure
   a. Dose of radiopharmaceutical
   b. Time(s) of acquisition postinjection
   c. Type of images (whole body, regional, SPECT)
3. Findings
   a. Site(s) of abnormal localization
   b. Degree of localization compared with liver, bone, or bone marrow uptake and whether it increased over time if delayed images were obtained
4. Study limitations or confounding factors
5. Impression (e.g. positive, negative, indeterminate)
   a. The clinical significance of the findings
   b. If appropriate, differential clinical diagnoses

J. 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 hemocytometer 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-gauge 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 hemocytometer slide. The average number of cells per 50-micron (small) square is then determined. No. of cells/cm^3 (mL) = average number of cells/small square × (2×10^6). This step is optional.

K. Sources of Error

1. Note that the normal biodistribution of ^{99m}Tc-leukocytes differs from that of ^{111}In-leukocytes. In adults, a changing pattern of bowel activity prior to 4 h is likely from intraluminal transit of labeled cells secondary to inflammatory bowel disease or bleeding, or may indicate a fistula from an abscess. In children, progressive physiologic bowel activity can be present by 1 h. Delayed imaging alone is often misleading in inflammatory bowel disease. Bone marrow expansion or hyperplasia can alter the normal marrow patterns. (See the Society of Nuclear Medicine Procedure Guideline for ^{111}In-Leukocyte Scintigraphy for Suspected Infection/Inflammation, section IV.J. for other sources of errors.)
2. False-negative results occur as a result of 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 before 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 h after injection.
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 h in children or 4 h 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 because of bleeding or noninfected reparative process.

V. Issues Requiring Further Clarification

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

VI. Concise Bibliography

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