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

version 2.0, approved February 7, 1999

Authors: Frederick L. Datz, MD (Retired, University of Utah Medical Center, Salt Lake City, UT); James E. Seabold, MD (University of Iowa Hospitals and Clinics, Iowa City, IA); Manuel L. Brown, MD (University of Pittsburgh Medical Center, Pittsburgh, PA); Lee A. Forstrom, MD, PhD (Mayo Clinic, Rochester, MN); Bennett S. Greenspan, MD (Harry S. Truman VA Medical Center, Columbia, MO); John G. McAfee, MD (George Washington Hospital, Washington, DC); Christopher J. Palestro, MD (Long Island Jewish Medical Center, New Hyde Park, NY); Donald S. Schauwecker, MD, PhD (Wishard Memorial Hospital, Indianapolis, IN); and Henry D. Royal, MD (Mallinckrodt Institute of Radiology, St. Louis, MO).

I. Purpose

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

II. Background Information and Definitions

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

III. Common Indications for Tc-99m 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 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 Indium-111 (In-111) leukocyte scintigraphy for detection of disease, particularly involving the small bowel. In-111 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 compared to chronic osteomyelitis.
   2. Combined In-111 white blood cell (WBC)/Tc-99m MDP bone and/or In-111 WBC/Tc-99m 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 Tc-99m WBC imaging.

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 i.v. 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 Tc-99m leukocyte localization in bone.
   2. Tc-99m labeled compared to In-111 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. In-111 leukocyte scintigraphy may be preferred in some patients with suspected sites of inflammation or infection in the abdomen/pelvis since, unlike Tc-99m leukocytes, there is normally no excretion into gastrointestinal or urinary tracts.
   4. In-111 leukocyte scintigraphy may be pre-
ferred 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 In-111 Leukocyte Scintigraphy for Suspected Infection/Inflammation.)

5. Ga-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 1½–2 hr and no later than 3–4 hr after obtaining the blood sample.
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 Use of Radiopharmaceuticals.)
1. Leukocytes are obtained from 20–40 ml of venous blood in adults. Circulating granulocyte counts should be a minimum of $2 \times 10^9$ 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

---

### Radiation Dosimetry for Adults

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Administered Activity (MBq/mCi)</th>
<th>Organ Receiving the Largest Radiation Dose (mGy/μSv (rad/rem))</th>
<th>Effective Dose (mSv/rem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m exametazime HMPAO-leukocytes</td>
<td>185 – 370 i.v. (5 – 10)</td>
<td>0.15 Spleen (0.56)</td>
<td>0.017 (0.063)</td>
</tr>
</tbody>
</table>

* Per MBq (per mCi)
*ICRP 53, page 232

---

### Radiation Dosimetry for Children (5 year old)

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Administered Activity (MBq/kg/mCi/kg)</th>
<th>Organ Receiving the Largest Radiation Dose (mGy/μSv (rad/rem))</th>
<th>Effective Dose (mSv/rem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m exametazime HMPAO-leukocytes</td>
<td>2.5 – 5.0 i.v. (0.07 – 0.14)</td>
<td>0.48 Spleen (1.8)</td>
<td>0.054 (0.20)</td>
</tr>
</tbody>
</table>

* Per MBq (per mCi)
*ICRP 53, page 232
not use methylene blue in this procedure.) For
details of cell labeling, see articles in bibliog-
raphy.
4. For adults, the usual administered activity is
185–370 MBq (5–10 mCi) of Tc-99m HMPAO
labeled white blood cells.
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 ex-
ceed the maximum administered activity for an adult.
6. Exametazime (HMPAO) is a lipophilic com-
plex which penetrates the leukocyte cell mem-
brane and is retained within the cell.
7. The spleen, bladder and large bowel receive
the largest absorbed radiation dose.
8. Leukocyte migration, chemotaxis, phagocyto-
sis, intracellular killing, adhesive and super-
oxide generation have been shown to remain
normal after labeling with Tc-99m HMPAO.

E. Image Acquisition

1. A large field of view gamma camera with a
low energy high resolution collimator is usu-
ally preferred. If count rates are poor on the
16–24 hr delayed images, a LEAP collimator
can be used. The pulse height analyzer is cen-
tered 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). (*See normal findings
IV.H.1.b.)
a. Regional images are obtained for at least
800,000 counts/large field of view or 5–10
min/view.
b. Whole-body images should include the an-
terior and posterior head, chest, abdomen,
pelvis and extremities when clinically indi-
cated. A limited study to evaluate a partic-
ular region of the body is acceptable in se-
lect cases.
3. Images of the limbs should be acquired for 10

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Early Imaging</th>
<th>Delayed Imaging</th>
<th>16-24 hour Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal abscess</td>
<td>0.5 – 1 hr for adults</td>
<td>Sequential to 4 hr</td>
<td>Rarely, if early images are negative, but requires longer imaging times</td>
</tr>
<tr>
<td></td>
<td>20 – 40 min for children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory or ischemic bowel dise</td>
<td>0.5 – 1 hr for adults</td>
<td>Sequential up to 4 hr; physiologic bowel activity may interfere on later images</td>
<td>Usually not indicated since physiologic bowel activity is present</td>
</tr>
<tr>
<td>disease</td>
<td>20 – 40 min for children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest-pulmonary infection</td>
<td>Physiologic lung activity may interfere</td>
<td>4 – 8 hr</td>
<td>If early images are negative, requires longer imaging times</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>May not have sufficient localization</td>
<td>4 – 8 hr</td>
<td>If early images are negative or equivocal (requires longer imaging times)</td>
</tr>
</tbody>
</table>
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 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 Tc-99m leukocytes is about 4 hr, and activity may be seen in the heart, lungs and great vessels, including the iliofemoral vessels even on delayed images (greater than 4 hr) due to slow clearance. In-111 leukocytes may be preferred for detection of vascular graft or dialysis shunt infection, since bloodpool 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 Tc-99m 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 to 30 min and usually increases in intensity over the next 2–3 hr.
      i. The degree and extent of bowel disease is usually demonstrated by 1–2 hr.
      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 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, post-irradiation changes, post-surgical 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 post-injection
   c. Type of images (total body, regional, SPECT)
3. Findings
   a. Site(s) of abnormal localization
   b. Degree of localization compared to liver, bone or bone marrow uptake, and does it increase 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 diagnosis

J. Quality Control
1. The labeling efficiency of Tc-99m 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 Tc-99m 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/cm³ (ml) = the average number of cells/small square x 2,000,000. This step is optional.

K. Sources of Error
1. Note that the normal biodistribution of Tc-99m leukocytes differs from In-111 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 the Society of Nuclear Medicine Procedure Guideline for In-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 Tc-99m 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. Non-infected vascular grafts and/or shunts can show increased localization due to bleeding or non-infected reparative process.

V. Issues Requiring Further Clarification
A. Relative efficacy of In-111 labeled leukocytes and Tc-99m labeled leukocytes in different clinical conditions
B. Radiation effects using Tc-99m doses greater than 20 mCi on granulocyte viability during Tc-99m HMPAO labeling procedure

VI. Concise Bibliography


Peters AM. The utility of Tc-99m HMPAO-leukocyte

**VII. 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 from 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.