# Technetium-99m(V)-DMSA and Gallium-67 in the Assessment of Bone and Joint Infection

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The aim of our study was to investigate the diagnostic value of scans with $^{99m}$Tc(V)-dimercaptosuccinic acid (DMSA) to localize bone and joint infection compared with scans using $^{67}$Ga. **Methods:** Thirty-six patients referred for investigation of bone and joint infection were studied. In all patients, a bone scan was obtained initially. Subsequently, comparative scans with $^{99m}$Tc(V)-DMSA and $^{67}$Ga were performed 1 wk apart. Microbiological findings, pathologic findings and/or clinical follow-up (until symptoms disappeared) were considered to be proof of the presence of bone and joint infection. **Results:** Technetium-99m (V)-DMSA showed greater sensitivity and accuracy than $^{67}$Ga in the assessment of bone and joint infection, although the difference was not statistically significant. **Conclusion:** In comparison with a $^{67}$Ga scan, a $^{99m}$Tc(V)-DMSA scan, in combination with a bone scan, is a reliable way to diagnose bone and joint infection. Both tracers were useful in the diagnosis of bone and joint infection.

**Key Words:** technetium-99m(V)-dimercaptosuccinic acid; gallium-67; bone and joint infection

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Bone and joint infection is often a diagnostic problem. Clinical symptoms are not always present and are often vague, and laboratory data are not very helpful. It is a serious health problem, because up to 15% of all patients with acute osteomyelitis develop chronicity (*1*). The outcomes depend on an accurate initial diagnosis. However, most studies lack adequate sensitivity and/or specificity. The sensitivity of plain radiography is 14%, and the specificity is 70% (*2*). Although very sensitive (92%–100%) for detecting infection, bone scintigraphy lacks specificity (60%–70%), because radiophosphate uptake in bone is a reflection of bone remodeling irrespective of the insult (*3*). However, the pinhole bone scan can be useful in specifically diagnosing bone and joint infection (*4,5*). Gallium-67 citrate is a classic tracer used for the detection of infection. However, it has some disadvantages, including its low specificity and poor target-to-background ratio. Leukocyte labeling is time consuming, complicated and costly. Conversely, $^{99m}$Tc is cheaper, has better physical characteristics, is more readily available and is more suitable for everyday clinical use.

We present a study to analyze the diagnostic value of $^{99m}$Tc(V)-dimercaptosuccinic acid (DMSA) compared with that of $^{67}$Ga in routine practice among patients with suspected bone and joint infection.

## MATERIALS AND METHODS

### Patients

By retrospective analysis of all $^{99m}$Tc(V)-DMSA and $^{67}$Ga scans performed in our department between 1994 and 1996, 36 patients (20 females, 16 males; age range 4–74 yr; mean age 53.5 yr) were studied. All patients were considered to have bone and joint infection. Each patient's hospital files were reviewed for clinical symptoms, diagnostic evaluation and therapy. None of the patients received antibiotic treatment before or during the radionuclide studies. All patients had a $^{99m}$Tc-methylene diphosphonate (MDP) bone scan before the $^{99m}$Tc(V)-DMSA and $^{67}$Ga scans. In our department, when the problem is suspected to be bone and joint infection, a bone scan is always required before the $^{99m}$Tc(V)-DMSA and $^{67}$Ga scans. Patients with no evidence of bone and joint infection on their bone scans were considered not to have bone and joint infection and were not investigated further with the $^{99m}$Tc(V)-DMSA and $^{67}$Ga scans. The final diagnosis was made by clinical follow-up (until symptoms disappeared), operative findings or bacteriological cultures. These cultures were obtained during surgery or through needle aspiration.

### Scintigraphic Evaluation

All scintigraphic studies were completed within 10 days. All patients had a $^{99m}$Tc-MDP bone scan before the $^{99m}$Tc(V)-DMSA and $^{67}$Ga scans. After intravenous administration of 740 MBq $^{99m}$Tc-MDP and 740 MBq $^{99m}$Tc(V)-DMSA, respectively, images were obtained 2–3 hr postinjection using a low-energy, parallel-hole collimator. The scintigraphic images of the $^{67}$Ga scan were taken 48 hr postinjection with 111 MBq $^{67}$Ga. A bone scan image was acquired before the $^{99m}$Tc(V)-DMSA and $^{67}$Ga studies. All scintigraphic images were interpreted by two nuclear medicine physicians blinded to all information other than a clinical suspicion of infection. A $^{99m}$Tc(V)-DMSA scan or $^{67}$Ga scan was considered positive for bone and joint infection if the area of increased tracer uptake on the $^{99m}$Tc(V)-DMSA scan or $^{67}$Ga scan was the same as the area with increased tracer uptake on the bone scan. A $^{99m}$Tc(V)-DMSA scan or $^{67}$Ga scan was considered negative for bone and joint infection if there was an absence of or no increased tracer uptake over the pathologic area seen on the bone scan. A scan was scored as true-positive if the increased radioactivity over the pathologic location was in agreement with operative findings, bacteriological cultures or clinical follow-up. A scan was judged as true-negative when there was no pathological tracer uptake over the affected lesion, and when there was no clinical or bacteriological evidence of bone and joint infection.

### Statistical Analysis

Statistical comparisons of sensitivities and specificities were performed with a Student's t-test, and a two-tailed p value of $< 0.05$ was considered statistically significant. The accuracy of the two tracers for diagnosing bone and joint infection was calculated and statistically compared using the McNemar test.

## RESULTS

The clinical characteristics, scintigraphic results and verification procedures are summarized in Table 1. The underlying abnormalities causing increased tracer accumulation were the presence of orthopedic devices (n = 1), joint prostheses (n = 5), previous fracture (n = 9) and recurrent infection (n = 5).

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**TABLE 1**
Clinical Details of Studied Patients

| Patient no. | Sex | Age | WBCC | Suspected focus | DMSA scan | Ga-67 scan | Previous pathology | ESR | Culture | Surg expl | Prob |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 7 | 15230 | Humerus | + | + | Fr | R | Pos | Pos | TP |
| 2 | M | 35 | 12700 | Tibia | + | + | Fr | R | NA | Pos | TP |
| 3 | M | 31 | 16200 | Femur | + | + | Fr | R | NA | Pos | TP |
| 4 | M | 67 | 9800 | Femur | − | − | Fr | NI | Neg | NA | TN |
| 5 | M | 39 | 11620 | T7-8 | + | + | Fr | R | Pos | Pos | TP |
| 6 | F | 42 | 7760 | L1-2 | + | + | Inf | R | Pos | NA | TP |
| 7 | M | 69 | 4110 | T11-12 | + | + | Inf | NA | Pos | NA | TP |
| 8 | M | 58 | 5750 | T-L spine | − | − | OD | NI | Neg | Neg | TN |
| 9 | F | 56 | 14930 | L2-3 | + | − | Inf | R | Neg | Pos | TP |
| 10 | F | 67 | 6350 | L5 | + | + | Inf | R | Pos | NA | TP |
| 11 | M | 42 | 8290 | Femur | + | + | Inf | R | Pos | Pos | TP |
| 12 | F | 58 | 12050 | Hip | + | + | OD* | R | NA | Pos | TP |
| 13 | F | 72 | 10210 | T11 | − | − | NI | R | Neg | NA | TN |
| 14 | F | 66 | 17350 | Hip | + | + | OD* | R | Pos | Pos | TP |
| 15 | F | 4 | 11002 | Knee | − | − | NI | R | Neg | NA | TN |
| 16 | F | 70 | 12070 | Knee | + | + | OD* | NA | Pos | NA | TP |
| 17 | M | 66 | 6480 | Knee | + | + | OD* | R | NA | Pos | TP |
| 18 | F | 52 | 6040 | Knee | − | − | NI | R | Neg | NA | TN |
| 19 | M | 63 | 7200 | Knee | + | + | NI | R | Pos | NA | TP |
| 20 | F | 66 | 12330 | Knee | + | + | NI | R | Pos | NA | TP |
| 21 | F | 62 | 8300 | Knee | − | − | NI | NI | Neg | NA | TN |
| 22 | M | 68 | 11680 | Femur | + | + | Fr | R | NA | Pos | TP |
| 23 | F | 40 | 7550 | L5 | − | − | NI | R | Neg | NA | TN |
| 24 | M | 30 | 7490 | Sacrum | − | + | Fr | R | Neg | NA | TN |
| 25 | F | 54 | 8800 | Hip | − | − | NI | NI | Neg | NA | TN |
| 26 | F | 72 | 5400 | Knee | − | − | NI | R | Neg | NA | TN |
| 27 | M | 53 | 6790 | Knee | − | − | NI | NI | Neg | NA | TN |
| 28 | F | 66 | 6400 | Knee | − | − | NI | R | Neg | NA | TN |
| 29 | F | 43 | 5300 | Ankle | + | + | NI | R | Pos | NA | TP |
| 30 | M | 67 | 6600 | Tibia | + | + | Fr | R | Neg | Pos | TP |
| 31 | M | 48 | 9600 | Tibia | + | + | Fr | R | Pos | Pos | TP |
| 32 | F | 74 | 6300 | Hip | − | − | OD* | R | Neg | NA | TN |
| 33 | F | 53 | 7200 | T-spine | − | − | NI | NI | Neg | NA | TN |
| 34 | F | 61 | 6720 | Spine | + | + | NI | R | Neg | NA | FP |
| 35 | F | 49 | 7310 | Spine | − | − | NI | R | Neg | NA | TN |
| 36 | M | 56 | 8800 | Ankle | + | + | NI | R | Pos | NA | TP |

WBCC = white blood cell count ($\times 10^9$/liter); DMSA = dimercaptosuccinic acid; ESR = erythrocyte sedimentation rate; Surg exp = surgical exploration; Prob = probability; + = positive; Fr = fracture; R = raised; Pos = positive; TP = true-positive; NA = not available; − = negative; NI = normal; Neg = negative; TN = true-negative; Inf = infection; OD = orthopedic devices; OD* = joint prosthesis; FP = false-positive.

The erythrocyte sedimentation rate was available in 33 patients; it was raised in 27 and normal in 6. The diagnosis was proven to be correct by surgical findings (n = 13) and bacteriological cultures (n = 31).

Infection was confirmed in 20 of 36 patients. Twenty of these infections were detected by the $^{99m}$Tc(V)-DMSA scan. The $^{67}$Ga scan diagnosed 19 and missed 1 (Patient 9), a case of chronic osteomyelitis. Figure 1 shows true-positive images from Patient 1 using both agents.

In 16 patients, infection was excluded. Technetium-99m(V)-DMSA scans correctly detected 15 patients, but in Patient 34 the scan was a false-positive because of the patient's bone metastasis (Fig. 2). The $^{67}$Ga scan agreed in 14 patients, but was false-positive in 2 patients. The first, Patient 24, recently had experienced a fracture of the sacrum, and the second, Patient 34, was suffering from bone metastatis.

Overall, there were 20 true-positive, 1 false-positive, 15 true-negative and 0 false-negative results with $^{99m}$Tc(V)-DMSA. With $^{67}$Ga, the figures were 19, 2, 14 and 1, respectively. Values for sensitivity, specificity and accuracy are presented in Table 2. Differences between the two agents were not statistically significant ($p > 0.05$).

## DISCUSSION

In suspected bone and joint infection, the diagnosis is usually made on the basis of clinical features, a radiograph and a bone scan. Radiography is based on x-ray absorption and reflects the mineral content of the bones. Bone destruction needs to be quite advanced to be visualized on a conventional radiograph with a bone mineral loss of about 50% (*6*).

The three-phase bone scan and, recently, the four-phase bone scan have been used widely to diagnose bone and joint infection (*7*). Unfortunately, their specificity is low in the presence of increased bone turnover. However, the three-phase bone scan can provide the important anatomical information required to interpret the images provided by $^{99m}$Tc(V)-DMSA and $^{67}$Ga scans. The aforementioned sensitivity is the reason why we always obtain a bone scan before $^{99m}$Tc(V)-DMSA and $^{67}$Ga scanning. If the bone scan is not normal in the affected area, we perform $^{99m}$Tc(V)-DMSA and $^{67}$Ga scanning to rule out or confirm bone and joint infection.

The agents used for the detection of focal inflammation/infection are $^{67}$Ga and white blood cells labeled with $^{111}$In (oxine or tropolone) or $^{99m}$Tc-hexamethyl propyleneamine oxime. Gallium-67 is a classic tracer used for the detection of

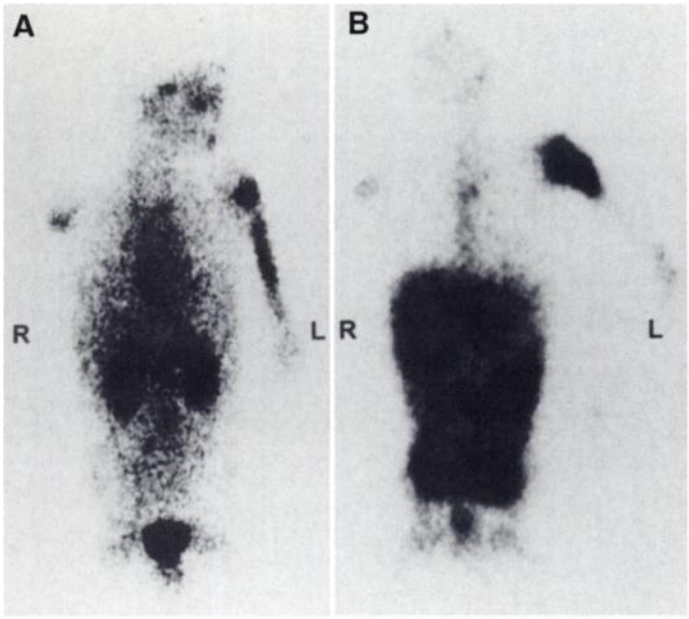


**FIGURE 1.** Scintigraphic images of 7-yr-old boy (Patient 1) with osteomyelitis in proximal humerus. (A) Anterior views of $^{99m}$Tc(V)-DMSA and (B) $^{67}$Ga scans showed uptake at same site and were interpreted as showing infection (true-positive study).

inflammation. However, multipeak, high-energy gamma rays, physiologic bowel excretion and nonspecific uptake in tumors and in areas of increased bone turnover make $^{67}$Ga a less optimal radiopharmaceutical for delineating infection (*8*). Leukocyte labeling is a time-consuming procedure (2–3 hr) and requires blood manipulation (difficulty in obtaining blood samples in some patients, risk of infection, etc.) (*9,10*). In addition, between 24 and 48 hr are required after administration of $^{67}$Ga to guarantee a good image, whereas with $^{99m}$Tc(V)-DMSA only 2–3 hr are necessary.

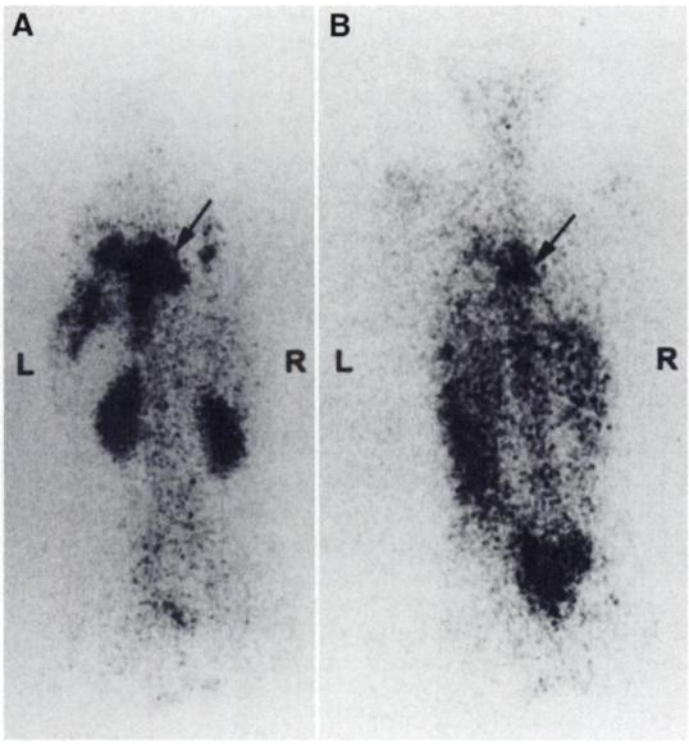


**FIGURE 2.** False-positive study in 61-yr-old woman (Patient 34). (A) Posterior views of $^{99m}$Tc(V)-DMSA and (B) $^{67}$Ga scans show accumulation of radiotracer in areas of bone metastases (arrow). Histologic specimens showed adenocarcinoma and culture was negative.

**TABLE 2**
Sensitivity, Specificity and Accuracy of Technetium-99m(V)-DMSA Scan and Gallium-67 Scan in Combination with Bone Scan, Respectively

| Tracer | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| $^{99m}$Tc(V)-DMSA | 100% | 93% | 97% |
| $^{67}$Ga | 90% | 93% | 92% |

DMSA = dimercaptosuccinic acid.

Technetium-99m(V)-DMSA, developed by Yokoyama et al. in 1981 (*11*), has been recognized as advantageous for the scintigraphic diagnosis of various malignant tumors and their metastasis (*12–15*). Ohta et al. (*16*) found that accumulation of $^{99m}$Tc(V)-DMSA was seen not only in malignant tumors, but also in benign tumors, fractures and osteomyelitis. In some inflammatory lesions, $^{99m}$Tc(V)-DMSA showed behavior similar to that of $^{67}$Ga, but the superior physical properties of $^{99m}$Tc(V)-DMSA and its lower cost justify use of $^{99m}$Tc(V)-DMSA. The localization mechanism of $^{99m}$Tc(V)-DMSA in tumor and inflammation is not well known. Ohta et al. (*17*) thought $^{99m}$Tc(V)-DMSA resembled the phosphate ion, because they found that it accumulated in tumors in which calcification was present, as indicated by pathology results. However, Clarke et al. (*18*) showed that $^{99m}$Tc(V)-DMSA is taken up into more sites than are visualized with $^{99m}$Tc MDP, suggesting that this may not be the explanation for the uptake. Physiological uptake has been demonstrated in breast tissues, kidneys, nasal mucosa and the blood pool (*19*). Consequently, further studies are needed to clarify the mode of uptake of $^{99m}$Tc(V)-DMSA.

The results of our study revealed that $^{99m}$Tc(V)-DMSA scans correctly identified 20 of 20 patients with bone and joint infection. These results were in agreement with previous studies where $^{99m}$Tc(V)-DMSA identified foci of infection (*16,20*). A false-positive scan was seen in 1 patient (Patient 34) with bone metastasis. The $^{99m}$Tc(V)-DMSA scan cannot discriminate the malignant from the benign, as suggested by Ohta et al. (*16*). There were 19 patients with a true-positive $^{67}$Ga scan and 14 patients with a true-negative scan. Two patients were considered to have had false-positive scans and 1 patient a false-negative scan. While $^{99m}$Tc(V)-DMSA and $^{67}$Ga demonstrated equal specificity, $^{99m}$Tc(V)-DMSA showed greater sensitivity and diagnostic accuracy (Table 2). In comparison with $^{67}$Ga scans, $^{99m}$Tc(V)-DMSA scan, in combination with a bone scan, is a reliable method to diagnose bone and joint infection.

## CONCLUSION

Technetium-99m(V)-DMSA scanning may be more sensitive and accurate than $^{67}$Ga scintigraphy for the diagnosis of bone and joint infection, though the differences shown in our study were not statistically significant. Technetium-99m(V)-DMSA has many advantages, such as low price, daily availability, good physical characteristics, no need for blood manipulation and an easy preparation procedure.Technetium-99m(V)-DMSA has potential for evaluation of bone and joint infection.

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# Chromium-51-EDTA Clearance in Adults with a Single-Plasma Sample

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In 1996, a committee on renal clearance recommended a mean sojourn time-based methodology for single-sample determination of plasma clearance of $^{99m}$Tc-diethylenetriamine pentaacetic acid (DTPA) to be used on adults if the patient's glomerular filtration rate (GFR) is suspected to be >30 ml/min. The main purpose of this study was to derive a mean sojourn time-based formula for calculation of $^{51}$Cr-ethylenediamine tetraacetic acid (EDTA) clearance in adults. **Methods:** Two groups of patients with $^{51}$Cr-EDTA clearance (Cl) between 16 and 172 ml/min were studied. In Group I (n = 46), reference Cl was determined as a multiplasma sample, single-injection method ($Cl_{SM}$). Sixteen blood samples were drawn from 0 until 5 hr after a single intravenous injection of $^{51}$Cr-EDTA. In Group II (n = 1046), reference Cl was determined by the Brøchner-Mortensen four-sample clearance method ($Cl_{BM}$). The plasma time-activity curves of Group I were used to derive two mean sojourn time-based formulas (Formulas 1 and 2) for calculation of a single-sample clearance. Formula 1 was derived from the entire time-activity curve, whereas the derivation of Formula 2 used only the final slope of the time-activity curve. The accuracy of the two formulas and the Christensen and Groth $^{99m}$Tc-DTPA formula was tested on Group II. **Results:** Chromium-51-EDTA Cl calculated by Formula 1 was almost identical to the Cl calculated by the reference Cl method (r = 0.982; $SD_{diff}$ = 5.82 ml/min). Both $^{51}$Cr-EDTA Cl calculated by Formula 2 and by the $^{99m}$Tc-DTPA formula showed close correlation with the reference method (r = 0.976, r = 0.985, respectively) but systematically overestimated GFR for the whole range of clearance values by 3.5 and 3.2 ml/min ($p < 0.001$), respectively. **Conclusion:** It is possible to get an accurate determination of $^{51}$Cr-EDTA Cl from a single-plasma sample in adults by the mean sojourn time methodology. The determination is marginally more accurate ($p < 0.001$) if using a formula derived from the entire plasma time-activity curve than from only the final slope. The single-sample formula derived for determination of $^{99m}$Tc-DTPA Cl tends slightly to overestimate GFR if used to calculate $^{51}$Cr-EDTA Cl.

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For the last decade, determination of the glomerular filtration rate (GFR) by single-plasma-sample technology has been increasingly accepted for clinical evaluation of GFR in adults. The first results indicating that it might be possible to determine GFR from the activity in one blood sample were provided by Fischer and Veall (*1*), who used a principle of "apparent volume of distribution" previously introduced by Tauxe et al. (*2*) for calculating effective renal plasma flow as $^{131}$I-orthoiodohippuran clearance. In 1981, Groth and Aasted (*3*) presented a nomogram for calculating $^{51}$Cr-ethylenediaminetetraacetic acid (EDTA) clearance that preceded the development of a theoretical method for calculating $^{51}$Cr-EDTA clearance from a single-plasma sample in children on the basis of the mean sojourn time of $^{51}$Cr-EDTA in its distribution volume (*4*). Today, numerous methodologies for calculation of single-sample GFR are available, and several of these have been compared by independent studies (*5–10*).

In 1996, a committee on renal clearance (*11*) recommended the mean sojourn time-based methodology applied for single-sample determination of plasma clearance of $^{99m}$Tc-diethylenetriamine pentaacetic acid (DTPA) by Christensen and Groth (*12*) to be used on adults if the patient's GFR was suspected to be more than 30 ml/min. It also acknowledged that $^{51}$Cr-EDTA is an acceptable alternative agent to $^{99m}$Tc-DTPA. Indeed, determining GFR by using $^{51}$Cr-EDTA, instead of $^{99m}$Tc-DTPA, remains the approach chosen by many laboratories in the world. The Christensen and Groth formula, however, has never been standardized for $^{51}$Cr-EDTA. Therefore, it is desirable that the mean sojourn time-based methodology also be developed to measure $^{51}$Cr-EDTA clearance in adults.

The purpose of this study was to use the single-plasma