
Sequential Technetium-99m HMDP–Gallium-67 Citrate Imaging for the Evaluation of Infection in the Painful Prosthesis

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In order to evaluate the clinical utility of sequential technetium-99m HMDP–gallium-67 scanning in patients with painful orthopedic prosthesis, a retrospective review was made of 154 sequential scans performed in 130 patients. Criteria for a positive study included spacially incongruent gallium–technetium uptake or gallium uptake that was congruent but more intense than technetium. Images were interpreted as negative if gallium was congruent and less intense than technetium. Sixty-six patients underwent surgery (31 infected, 35 aseptic), and 64 were evaluated clinically (3 infected, 61 aseptic). The combined results of the surgical and nonsurgical patients yielded a sensitivity of 66%, a specificity of 81%, and an accuracy of 77%. In this series, the technetium–gallium scan combination has proven to be helpful but more recent techniques such as indium-111-labeled leukocytes may prove to be superior to sequential technetium–gallium imaging.

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The success of total joint arthroplasty has been well documented. It is estimated that over 150,000 prostheses are now implanted yearly. However, these procedures are not without complication, sepsis and aseptic component loosening being among the most common. In the patient with a painful prosthesis, differentiating septic from aseptic component loosening is often a difficult diagnostic problem (1–4). Appropriate treatment depends upon correct preoperative diagnosis.

Several studies have suggested that sequential technetium-99m–gallium-67 (Tc–Ga) scanning is extremely accurate in delineating periprosthetic sepsis from aseptic component loosening (5,6). However, more recent reports suggest that sequential Tc–Ga imaging is much less accurate than originally proposed (7–9). We are reporting our experience with sequential Tc–Ga imaging in evaluating patients with painful orthopedic prostheses. The specific aim of this study was to assess the accuracy and clinical utility of sequential Tc–Ga imaging to define infection in this rather difficult clinical situation.

MATERIALS AND METHODS

We retrospectively reviewed the charts of all patients who had sequential Tc–Ga images performed from September 1975 to December 1981. One hundred and fifty-four sequential scans were performed in 130 patients for evaluation of a possible infection in a painful prosthesis. Each chart was carefully reviewed, recording the presenting signs and symptoms, laboratory data, and roentgenographic findings. In instances where hip aspiration and arthrogram were performed these results were also noted.

In patients who underwent surgery, histology and microbiologic data were utilized to establish the final diagnosis. Histology was considered positive for sepsis if five or more polymorphonuclear leukocytes or ten or more lymphocytes were present per high power field (10). Tissue cultures were considered positive for infection if organisms grew on solid media. In instances where organisms grew in broth media only, histologic evaluation of surgical tissue specimens was utilized to establish the diagnosis. In all cases tissue specimens were cultured for anaerobic and aerobic organisms as well as fungi. All patients who did not have surgical confirmation of the diagnosis were followed for an average of 2 yr following imaging. These patients were

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then classified as septic or nonseptic according to clinical course and treatment at final follow-up.

The sequential Tc–Ga images at our institution utilized a variety of large-field-of-view gamma cameras with low-energy, high-resolution collimation for technetium-99m imaging and a medium energy collimation for gallium-67 imaging. Twenty millicuries of technetium-99m hydroxymethylene diphosphonate (^{99m}Tc]HMDP) was injected intravenously with imaging at 3–4 hr postinjection. The gallium scan utilized 5 mCi of gallium-67 citrate and images were performed at 24 and 48 hr postinjection. Images were interpreted in a blind, randomized fashion without any knowledge of the roentgenographic, laboratory, clinical, or surgical data. Sequential Tc–Ga images were considered positive for infection if gallium and technetium uptake was spatially incongruent (Fig. 1) or if gallium uptake was congruent and more intense than technetium. Images were interpreted as negative if gallium was congruent and less intense than technetium (Fig. 2). In instances where gallium and technetium uptake were congruent and of similar intensity, the image was recorded as equivocal.

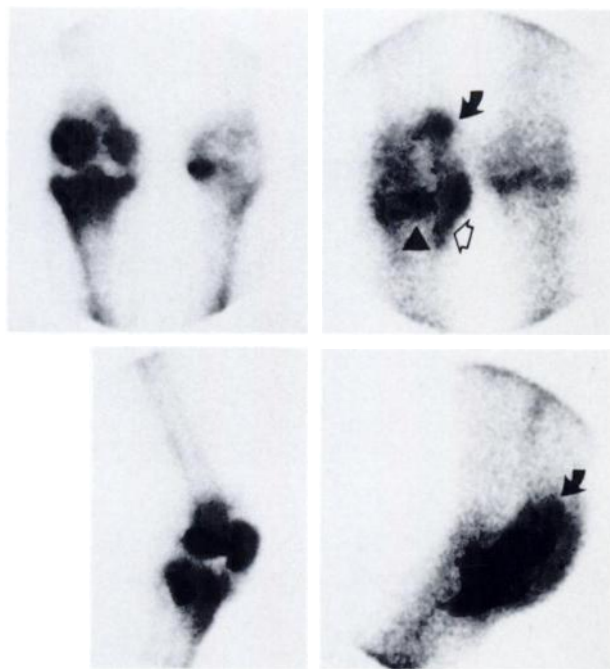


FIGURE 1
Total knee arthroplasty. Left upper and lower panels: ^{99m}Tc]HMDP bone scan of knee. Right upper and lower panels: ^{67}Ga images of knee. Curved arrow demonstrates noncongruent gallium activity in suprapatella bursa. Open arrow demonstrates incongruent activity along medial aspect of tibia. Arrowhead demonstrates relative increased activity of gallium over technetium in mid-tibial region. On operation there was infection in suprapatella bursa, soft tissues adjacent to tibia, and area of osteomyelitis in both central and medial portion of tibial component

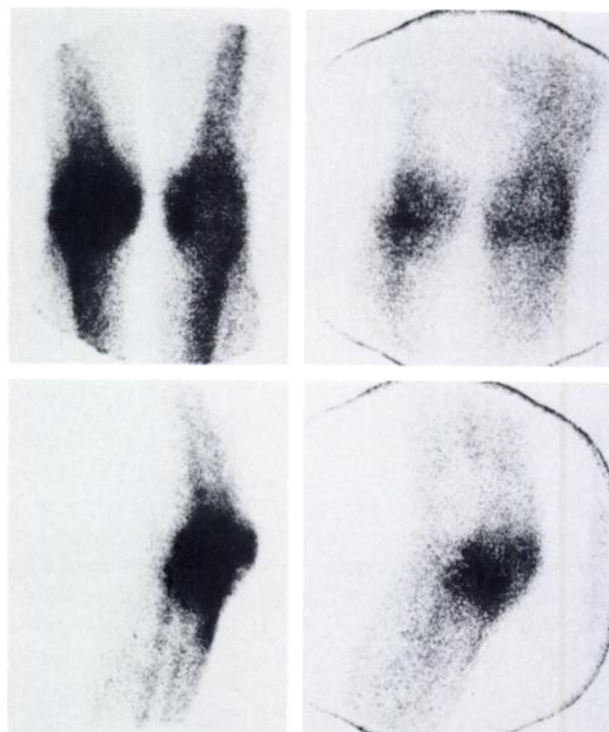


FIGURE 2
Right total knee arthroplasty. Left upper and lower panels: ^{99m}Tc]HMDP. Right upper and lower panels: ^{67}Ga images. Focal area of gallium uptake in midportion of knee arthroplasty is less intense than technetium. There was no evidence of infection at surgery

RESULTS

Patient Profile and Clinical Data

Of these 130 patients, 66 were male and 64 female with the average age being 58 yr (range 29–83 yr) at the time of prosthetic implantation. The average time from surgery to the time of sequential Tc–Ga scanning was 42 mo (range 8–143 mo). Forty-eight of these surgical procedures were performed at our institution, with the remaining 82 performed elsewhere. Of the 154 sequential Tc–Ga images performed for painful prosthesis, four were considered technically inadequate and excluded. Of the remaining 150 patients, imaging was performed for: 71 total hip arthroplasties (THA); 27 girdlestone procedures following removal of a previously infected THA; 14 total knee arthroplasties (TKA); eight hip endoprotheses; eight hip screw compression devices; one total elbow arthroplasty (TEA); and one total ankle arthroplasty (TAA).

Only 11 patients had a history of prior fever and all patients were afebrile at the time of presentation. On examination, 22 patients had local signs of possible sepsis (i.e., swelling, erythema, tenderness), of which 15 presented with or had history of draining sinus tract. Virtually all patients had pain with ambulation result-

ing in variable restriction in activity. Night pain or pain at rest was noted in 41 patients.

Diagnosis and Surgical Findings

Sixty-six patients underwent surgery and 64 did not. Of the 66 undergoing surgery, 27 had removal of the prosthesis only, 18 had a girdlestone resection arthroplasty converted to THA, 12 THA patients had revision of both components, six THAs had revision of the femoral component, and two had revision of the acetabular component only. One patient underwent exploration for possible aseptic component loosening but both components were found to be solidly fixed. Removal of the broken trochanteric wires provided symptomatic relief for this patient.

Of the 66 patients who underwent surgery, 31 had positive tissue cultures and histology and 35 had no evidence of sepsis by microbiologic or histologic examination. Three of the 35 aseptic patients had positive hip aspiration but negative tissue cultures of operative specimens. The organisms recovered were *Staphylococcus epidermidis* or *Propionibacterium acnes* in broth only, but not on solid media. These cultures were considered contaminants. Thus, 31 patients were diagnosed as infected and 35 as aseptic.

The remaining 64 patients who did not have surgery were followed for 2 yr to establish the diagnosis. Three of these patients were thought to be infected. One patient had positive culture on solid media following hip aspiration and was treated with antibiotics with a satisfactory result 18 mo later. Two other patients were thought to be septic but refused surgery. These two patients subsequently had revision surgery for septic prostheses at other institutions. In the remaining 61 patients, 59 had no clinical, laboratory, or roentgenographic findings to support an infectious process. The remaining two patients had a previous draining sinus which had healed, but otherwise no evidence of an inflammatory process.

Laboratory and Roentgenographic Findings

The average white blood count was $6.5 \times 10^3/\mu\text{ml}$ (range 2.8–17.9) with an average differential having 63% neutrophils (range 38–90%). Only ten patients had elevated white blood cell counts ($>10.9 \times 10^3/\mu\text{ml}$) of which five were infected and five were not. Of those 14 patients with $>75\%$ neutrophils, nine were infected. Thus, an elevated white blood cell count had no predictive value but a predominance of neutrophils suggested possible infection. In the 118 patients with a sedimentation rate the average value was 26 Westergren units (range 1–161), and 32 patients had a sedimentation rate of >40 . Seventeen of these 32 patients were found to be infected at surgery and 15 were not infected, although only five of these aseptic patients underwent surgery. The remaining 14 patients found to have septic prostheses at surgery all had sedimentation rates of <35 , as

did the three patients thought to be infected in the nonsurgical group.

Roentgenograms were evaluated for component migration, bone-cement and cement-prosthesis interface radiolucency, cement fractures, calcar resorption, endosteal cavitation, cortical thickening, and periosteal reaction. Of all these radiographic findings only endosteal cavitation appeared to suggest a septic process as nine of the 17 patients with this sign were found to be septic.

Forty-one patients with joint replacement had aspiration of the involved joint with anaerobic and aerobic cultures of the aspirate. Hip aspiration correctly identified the causative organism by growth on solid media in eight patients, and accurately ruled out infection in 19 patients. However, 11 patients had positive culture and histology at the time of surgery and were thus incorrectly diagnosed as aseptic by culture at the time of aspiration despite the noting of fluid present at the time of aspiration. As previously mentioned, three patients had positive cultures in broth only, which we feel were contaminants. Thus, although a positive culture on solid media certainly makes the diagnosis of sepsis, a negative culture by no means rules out a periprosthetic infectious process.

Radionuclide Imaging

Patients who had clinical diagnosis of infection were considered separately from those patients who had surgical confirmation of the diagnosis of infection.

In six of the 66 patients who underwent surgery the sequential Tc–Ga scan was interpreted as equivocal. The results of the remaining 60 patients were: 18 true positives, 26 true negatives, seven false positive and nine false negative scans. Nine of the 64 patients in the nonsurgical group had equivocal scans. Of the remaining 55 patients we found: one true positive, 44 true negatives, nine false positive and one false negative scan. These results are summarized in Table 1. Sensitivity, specificity, accuracy, predictive value (+) test, and predictive value (–) test were calculated and recorded (Table 2).

In analyzing the date from the surgical groups, ten of the 60 scans had spatially incongruent gallium uptake

TABLE 1
Summary of Image Results Excluding Equivocal Scans

	Diagnosis	Scan interpretation	
		+	–
Surgical group	Infected	18	9
	Not infected	7	26
Nonsurgical group	Infected	1	1
	Not infected	9	44

TABLE 2
Results of Combined Tc-Ga Scanning

	Surgical (No. 66) (%)	Nonsurgical (No. 64) (%)	Combined (No. 130) (%)
Sensitivity	66.7	50	66
Specificity	78.8	83	81
Accuracy	73.3	81.8	77
Predictive value (+) test	72	10	54
Predictive value (-) test	74.3	97.7	88

compared with technetium. In those ten patients, the sequential Tc-Ga scan result was nine true positive and one false positive. In the remaining 50 scans in this group, a congruent technetium-gallium pattern was observed and thus were much more difficult to read. The results of these 50 scans were: nine true positives, 26 true negatives, six false positives, and nine false negatives. Congruent patterns in which mild-moderate gallium uptake was found were particularly difficult to interpret. In six patients (10%), the intensity of gallium and technetium uptake was so similar that we could not decide on a diagnosis and these images were classified as equivocal.

DISCUSSION

The indolent nature of periprosthetic sepsis has been noted by several investigators (1-4,11-12). The clinical signs and symptoms associated with inflammation are commonly absent. Laboratory tests are usually of little value. Roentgenograms are distorted due to previous surgery and generally are not diagnostic of infection. Thus, a noninvasive technique to accurately diagnose septic from aseptic prosthetic component loosening would be helpful.

The technetium bone scan is quite sensitive in recognizing an inflammatory osseous process (13-15); however, the technetium bone scan cannot differentiate septic from aseptic component loosening. Although a number of reports attest to the high accuracy of sequential Tc-Ga imaging, these studies frequently involve small numbers of patients, without surgical confirmation of the diagnosis, or were performed on patients with overt signs of sepsis.

Our group of patients represents the difficult diagnostic dilemma often presented by the patient with a painful prosthesis. The large majority of these patients had no clinical or laboratory evidence enabling differentiation of a septic from a nonseptic process. Although hip aspiration correctly identified eight patients who were infected, 11 patients found to be infected at surgery had negative cultures of a hip aspiration. Roentgenograms were not diagnostic although endosteal scalloping suggests sepsis.

The accuracy rate of 73% with sequential Tc-Ga scanning in the 66 patients who underwent surgery is similar to more recent reports, but in contrast with others. Reing et al. (16) reported on 79 patients with sequential Tc-Ga imaging of which he reported 19 true positives, 59 true negatives, one false negative, and no false positives. This would give an accuracy rate of 99%. However, he included no criteria for scan interpretation, did not have tissue specimens for histologic evaluation, and did not report the clinical presentation of these patients. Forty-six patients with orthopedic devices were studied by Rosenthal et al. (9); however, only 17 had the diagnosis established by surgery. Furthermore, they described "mild and moderate" gallium uptake in 15 patients that had a congruent spatial pattern, but classified these patients as aseptic. These authors did note that gallium accumulates in areas of increased bone metabolism and reactive bursa, and they demonstrated gallium accumulation at a pseudarthrosis. Horozowski and associates (6) recommended sequential Tc-Ga imaging differentiation between mechanical loosening and loosening secondary to an infectious process. However, of 14 patients, they had two false positive images, two scans interpreted as equivocal, six patients with draining fistula and overt signs of clinical sepsis, and presumed diagnosis without surgical material in some patients. Williams et al. (17) found that gallium scanning with technetium was valuable in recognizing an infection following total hip arthroplasty. However, of 14 patients classified as infected following surgery, only three had positive cultures. Additionally, eight of these 14 infections had draining sinuses. These authors also report one false negative and two false positive gallium scans.

La Manna et al. (8) recently reported the results with sequential Tc-Ga scanning in 60 patients with painful total joint arthroplasties. Forty-one patients had surgical diagnoses. Their results were 24 false positive gallium scans and two false negatives for an overall accuracy rate of 57%; however, scan interpretation criteria was not included. The use of digital subtraction imaging in patients with sequential Tc-Ga scans for painful prosthetic joints was detailed by Hattner and associates (7). Of 92 patients with culture diagnosis, 53 who had surgery, they reported three false-negative gallium scans and 23 false positives resulting in an accuracy rate of 72%.

Our findings are in agreement with these more recent reports. In the surgically confirmed cases the accuracy rate was 73%, similar to that of Hattner et al. (7). Although in those patients with only clinical diagnoses the accuracy improved to 82%, this improvement may very well be due to incorrect diagnosis. These results are also similar to a recent article by Rosenthal and colleagues (18). In this review of 223 patients referred with a presumptive diagnosis of osteomyelitis, the sequential technetium-gallium scan had a sensitivity of

72%, a specificity of 86%, and an accuracy of 80%. Their scan interpretation criteria B was similar to that used in our study. When only the 18 patients with violated bone were evaluated, the sensitivity of the Tc-Ga exam was 77% (18).

This study also confirms the relatively little value of laboratory and roentgenograms in differentiating periprosthetic sepsis from aseptic prosthetic loosening. Although elevated sedimentation rates are suggestive of infection, 14 patients with surgically proven sepsis had normal values and 15 of the 32 patients with elevated sedimentation rates were not found to have any evidence of infection at the time of surgery. Of the 19 patients with hip aspiration and found infected at surgery, eight had culture-positive aspiration and 11 did not. Thus, although a positive aspiration accurately identifies an infectious process, a negative aspiration by no means excludes periprosthetic sepsis.

The high sensitivity but nonspecificity of technetium scintigraphy is well known. The addition of gallium scanning was thought to increase the specificity for infectious processes. However, a number of articles have documented increased gallium accumulation in nonseptic processes such as areas of sterile inflammation and nonunion (19-22). Gallium uptake has been found to concentrate at similar levels in aseptic periosteal new bone and osteomyelitic bone (23). This nonspecific uptake of gallium makes differentiation of sepsis from aseptic component loosening by sequential Tc-Ga scanning difficult. Patterns in which gallium uptake is not congruent to technetium uptake were accurate in nine out of ten surgical patients. However, the large majority of patients exhibited congruent technetium-gallium patterns. Under these circumstances we found the sequential Tc-Ga scans accurate in 70% of cases and equivocal in 10%.

Since periprosthetic sepsis often presents insidiously, a noninvasive method of detection is needed to select appropriate treatment. Sequential Tc-Ga imaging has proven helpful, but was only 73% accurate in 66 patients with surgical diagnosis. The search continues for more specific agents to identify areas of musculoskeletal sepsis. More recent techniques may prove superior to sequential Tc-Ga imaging.

FOOTNOTE

* General Electric, Milwaukee, WI, Ohio Nuclear, Solon, OH (now Technicare Corp.), and Searle, Chicago, IL.

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