The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/14865

Please be advised that this information was generated on 2019-04-16 and may be subject to change.
Evaluation of Infectious Diabetic Foot Complications with Indium-111-Labeled Human Nonspecific Immunoglobulin G


Departments of Nuclear Medicine, Internal Medicine, Radiology, and Surgery, University Hospital Nijmegen, Nijmegen, The Netherlands

Osteomyelitis of the foot is a well-known complication of diabetes mellitus. In this study, the validity of $^{111}$In-labeled human nonspecific immunoglobulin G (IgG) scintigraphy was studied in 16 diabetic patients with foot ulcers, gangrene or painful Charcot joints. In all patients, plain radiographs, conventional bone scan images and $^{111}$In-IgG images were recorded. The results were verified by histologic examination of surgical specimens in patients who did not respond to antibiotic treatment within 2–3 wk (10 lesions) or long-term clinical follow-up of at least 6 mo (16 lesions). On the bone scans, all seven osteomyelitic foci were detected. However, 19 additional foci not due to osteomyelitis were seen. The absence of true-negative bone scans in this study resulted in a specificity of 0%. On the plain radiographs, four of seven osteomyelitis foci were detected; for $^{111}$In-IgG scintigraphy, six of seven (sensitivity 57% and 86%, respectively). Plain radiographs correctly ruled out osteomyelitis in 15 of 19 lesions, $^{111}$In-IgG scintigraphy in 16 of 19 (specificity 79% and 84%, respectively). All imaging procedures gave false-positive results in penetrating ulcers over the calcaneus in two patients and in one patient with a Charcot joint, most likely due to recent fractures. A false-negative $^{111}$In-IgG study was observed in a patient with severe arterial angiopathy. Accurate estimation of probable osteomyelitis was not possible from the results of soft-tissue cultures, since in only 6 of 12 positive cultures, osteomyelitic foci could be proven. Indium-111-IgG scintigraphy can contribute to adequate evaluation of osteomyelitis in diabetic foot complications because it improves specificity when compared to bone scan and radiographic findings and improves sensitivity in comparison to plain radiographs.


Infection of the foot is a serious complication of long-existing diabetes mellitus, increasing patient morbidity and mortality considerably. Clinical assessment of the extent of infection is difficult because of concomitant neuropathic and angiopathic changes. Roentgenological findings are nonspecific (1). Bone scintigraphy with $^{99m}$Tc-methylene diphosphonate (MDP) is highly sensitive, but lacks sufficient specificity (2,3). Gallium-67 scintigraphy provides disappointing results, mainly due to accumulation in areas of increased bone turnover that are not infected (4,5). Better results have been reported using labeled leukocyte (WBC) scintigraphy (6,7). The time-consuming and relatively difficult preparation of labeled WBC is a major drawback for widespread use of this technique. Recently, the potential of $^{111}$In-labeled human nonspecific immunoglobulin G (IgG) scintigraphy for diagnosing infectious bone and joint disease was reported (8–10).

The aim of this study was to evaluate the utility of $^{111}$In-IgG scintigraphy in diabetic patients with suspected osteomyelitis of the foot.

PATIENTS AND METHODS

Patients

Sixteen patients (eight male, eight female) with diabetes mellitus (13 type II and 3 type I) were studied. Mean age was 62.1 yr (range, 41–83 yr). Mean duration of the diabetes was 21.3 yr (range, 5–42 yr).

All patients suffered from ulcers, gangrene or a painful Charcot joint. The latter was defined according to Levin: a deformed foot (particularly of the tarsal and metatarsal bones), increased temperature and erythema (11).

Patients with severe foot infection requiring immediate surgical intervention were excluded. Since $^{99m}$Tc-MDP bone scintigraphy has excellent sensitivity for the detection of osteomyelitis, patients with normal bone scans were also excluded. No patient had a history suggestive of severe systemic reaction after prior IgG administration or of IgG or IgA deficiency.

Clinical Assessment

Inspection and Soft-tissue Cultures. The location of ulcers and gangrene was noted. To obtain material for cultures, a tissue curettage from the base and edges of all ulcers and gangrenous lesions was performed according to the method described by Lipski et al. (12). The material was placed in a sterile container...
Angiopathy. In patients complaining of intermittent claudication, the maximum pain-free walking distance was recorded. Pedal pulses were palpated. Systolic blood pressure was measured in the dorsal pedal and posterior tibial arteries using a conventional 10 MHz Doppler ultrasound probe (Stopler, Parks Electronics Lab) and an occluding leg cuff. Measurements were made until three reproducible values were obtained (within a range of 10 mmHg). The mean of these readings was calculated. The brachial systolic blood pressure was measured in the same way using an arm cuff. The ankle/brachial pressure index (A/B index) was calculated (13,14). Since medialcalcification may cause falsely elevated blood pressure measurements, presence or absence thereof was noted on radiographs of the feet (15).

Neuropathy. Neuropathic symptoms had to be present for at least 6 mo. The vibration sense was tested with a 128 Hz tuning fork on the first metatarsal and lateral ankle of both feet. This test was performed three times on both locations. Results were categorized as: (a) normal, (b) diminished on the toes only, (c) absent on the toes and diminished on the ankle and (d) absent on both the toes and the ankle.

Knee and ankle reflexes were categorized as either normal or absent/diminished.

Radiopharmaceutical

Human nonspecific polyclonal IgG (Sandoglobulin, Sandoz AG, Nuernberg, FRG) was conjugated to diethylenetriaminepentaacetic bicyclic anhydride (bicyclic DTPA) according to the method described by Hnatowich et al. and labeled with 111In (Indium chloride, Amersham International Ltd., Buckinghamshire, UK) (16). Labeling efficiency was always higher than 95%. A dose of 1–2 mg of IgG labeled with 75 MBq 111In was injected intravenously.

Imaging Protocol

Plain radiographs of the feet were made in all patients. All scintigraphic images were obtained with a Siemens Orbiter gamma camera connected to a Scintiview image processor (Siemens Inc., Hoffman Estate, IL) equipped with a low-energy, all-purpose collimator for 99mTc-MDP bone scintigraphy or a medium-energy parallel-hole collimator for 111In-IgG scintigraphy.

A four-phase bone scintigraphy was performed using 600 MBq 99mTc-MDP. Immediately after injection, dynamic images of the feet (3 sec per image) were obtained for 1 min. At 5 min postinjection (p.i.), a so-called blood-pool image (350 kcts) was made. After 3 hr, delayed images of the feet (anterior, plantar, lateral, and medial view) were made with a preset time of 5 min each. An additional plantar image for a preset time of 15 min was obtained 24 hr p.i. in order to obtain optimal bone delineation.

Indium-111-IgG was injected immediately after the 24-hr p.i. bone scan image was recorded. Indium-111-IgG images were made 4, 24, and 48 hr p.i. At all time points, images of the feet were obtained from four angles. All images were collected for a preset time of 10 min. The 4-hr images were recorded using only the 247 keV photopake with a 15% symmetrical window in order to avoid 99mTc scatter in areas with significant 99mTc-MDP retention. Both the 173 and 247 keV peaks of 111In with a 15% symmetrical window were used to record the images at 24 and 48 hr p.i.

Image Interpretation and Verification

The conventional radiographs of the feet were reviewed by an experienced radiologist who was unaware of the clinical and scintigraphic findings. The radiographs were assessed for osteomyelitis using criteria as given by Resnick (in ascending order of relevance: soft-tissue swelling, osteoporosis, osteolysis, cortical or medullary destruction and sequestration) (17). A diagnosis was made as positive, negative or equivocal. A radiograph was considered equivocal for osteomyelitis when the findings of major relevance (cortical/medullary destruction and sequestration) were not observed.

All scintigraphic images were interpreted by three observers unaware of the results of clinical and roentgenological findings. The bone scan was considered positive for osteomyelitis when pathologic uptake was observed on both early phases (dynamic images and/or blood-pool images) and the late images. Indium-111-IgG scintigraphy was considered positive when focal with time increasing accumulation was observed. With bone scintigraphy used as a landmark, increased 111In-IgG uptake was attributed to either bone or soft-tissue by visually superimposing the 111In-IgG image on the bone scan image. The bone scan alone did not contribute to the diagnosis of osteomyelitis.

Patients whose ulcers showed no tendency of healing or whose complaints did not disappear with antibiotic medication and local treatment within 2–3 wk underwent surgery. For these patients, material was collected for histologic examination. Leukocyte and bacterial infiltration of bone tissue was considered to be histologic proof of osteomyelitis. For patients who responded well to antibiotic medication and local treatment, the data obtained during follow-up of at least 6 mo were used to judge the results of the radiographs and the scintigraphic images.

RESULTS

Table 1 shows the individual clinical data for the patients and a description of their foot problem. Only the A/B index of the diseased foot is included in the table. All patients had evidence of neuropathy. Six patients also showed signs and symptoms of angiopathy.

Table 2 shows the results of the radiographs and scintigraphic images with regard to ossal involvement and the results of the verification procedures in the individual patients. At the time of imaging, nine patients (nos. 4, 6, 7, 8, 11, 12, 13, 14 and 16) were treated with flucloxacillin (dose, 2–6 g daily) for a short period of time (mean 3 days, range 1 to 6 days). No other antibiotics were used.

Technetium-99m-MDP Bone Scan

As indicated in Tables 1 and 2, in all 22 localizations clinically suspect for osteomyelitis, increased 99mTc-MDP uptake was observed. The bone scan revealed four additional possible osteomyelitic foci. All seven proven osteomyelitic lesions could be identified on the bone scan. The remaining nineteen areas of increased uptake were not due to osteomyelitis, but were caused by neuropathic osteopathy, Charcot joints, degenerative osteoarthritis, uninfected pressure points and soft-tissue involvement with local hyperperfusion.
### TABLE 1
Clinical Characteristics, Duration of Diabetes Mellitus, Signs and Symptoms of Diabetic Neuropathy and Angiopathy, Localization of the Ulcer of Necrosis and Results of Soft-tissue Cultures

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>(Sex/Age)</th>
<th>Neuropathy</th>
<th>Angiopathy</th>
<th>Localization (clinical) (soft-tissue culture)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(M/65)</td>
<td>Numbness in toes, absent VS (toes), absent KR, AR</td>
<td>No claudication, normal pulsations, A/B index 1.08</td>
<td>Ulcer first toe L (culture negative)</td>
</tr>
<tr>
<td>2</td>
<td>(F/76)</td>
<td>Numbness in feet, absent VS absent KR, AR</td>
<td>No claudication, normal pulsations, A/B index 0.59</td>
<td>Ulcer midfoot R (culture: Proteus and beta-hemolytic Streptococcus)</td>
</tr>
<tr>
<td>3</td>
<td>(F/56)</td>
<td>Numbness in toes, absent VS (toes), normal KR, absent AR</td>
<td>No claudication, normal pulsations, A/B index 0.98</td>
<td>Ulcer heel L (culture: Staphylococcus epidermidis)</td>
</tr>
<tr>
<td>4</td>
<td>(M/83)</td>
<td>Numbness in feet, absent VS, absent KR, AR</td>
<td>Claudication (1000 m), absent pulsations, A/B index 0.47</td>
<td>Ulcer second toe R (culture: beta-hemolytic Streptococcus)</td>
</tr>
<tr>
<td>5</td>
<td>(F/81)</td>
<td>Numbness in feet, absent VS, absent KR, AR</td>
<td>No claudication, normal pulsations, mediacalciﬁcation, A/B index 1.10</td>
<td>Gangrene in second toe R (culture: mixed flora including anaerobic bacteria); ulcer hindfoot R; Charcot joint L and R</td>
</tr>
<tr>
<td>6</td>
<td>(F/77)</td>
<td>Numbness in lower legs, absent VS, absent KR, AR</td>
<td>No claudication, absent pulsations, A/B index 0.44</td>
<td>Ulcer first toe R (culture: Staphylococcus aureus and beta-hemolytic Streptococcus)</td>
</tr>
<tr>
<td>7</td>
<td>(F/55)</td>
<td>Numbness in toes, absent VS, absent KR, AR</td>
<td>No claudication, normal pulsations, A/B index 0.92</td>
<td>Ulcer second toe R (culture: Staphylococcus aureus)</td>
</tr>
<tr>
<td>8</td>
<td>(F/63)</td>
<td>Numbness in lower legs, absent VS, absent KR, AR</td>
<td>Claudication (100 m), absent pulsations, mediacalciﬁcation, A/B index 0.53 (R), 0.74 (L)</td>
<td>Ulcer midfoot L and R (culture: Staphylococcus aureus and Enterobacter species)</td>
</tr>
<tr>
<td>9</td>
<td>(F/59)</td>
<td>Numbness in feet, pain, absent VS, absent KR, AR</td>
<td>No claudication, normal pulsations, mediacalciﬁcation, A/B index 0.93 (R), 0.87 (L)</td>
<td>Charcot joints L and R (culture not done)</td>
</tr>
<tr>
<td>10</td>
<td>(M/45)</td>
<td>Numbness in feet, pain, absent VS (ankle), normal KR, absent AR</td>
<td>No claudication, normal pulsations, mediacalciﬁcation, A/B index 1.87</td>
<td>Charcot joint L (culture not done)</td>
</tr>
<tr>
<td>11</td>
<td>(M/63)</td>
<td>Paresthesia, absent VS, absent KR, AR</td>
<td>Claudication (500 m), absent pulsations, A/B index 0.39 (R), 0.39 (L)</td>
<td>Ulcer midfoot L (culture: Morganelli morganni)</td>
</tr>
<tr>
<td>12</td>
<td>(M/58)</td>
<td>Numbness in feet, absent VS, normal KR, absent AR</td>
<td>Claudication (10 m), absent pulsations, A/B index 0.39</td>
<td>Gangrene fourth and fifth toe R (culture: Staphylococcus aureus)</td>
</tr>
<tr>
<td>13</td>
<td>(M/72)</td>
<td>Absent VS (toes), normal KR, absent AR</td>
<td>Claudication (50 m), absent pulsations, mediacalciﬁcation, A/B index 0.52</td>
<td>Ulcer first toe L (culture negative)</td>
</tr>
<tr>
<td>14</td>
<td>(M/55)</td>
<td>Numbness in feet, absent VS, absent KR, AR</td>
<td>No claudication, normal pulsations, A/B index 1.21</td>
<td>Ulcer heel R (culture: Staphylococcus aureus and epidermidis)</td>
</tr>
<tr>
<td>15</td>
<td>(M/44)</td>
<td>Numbness in feet, absent VS (toes), normal KR, absent AR</td>
<td>No claudication, normal pulsations, mediacalciﬁcation, A/B index 0.77</td>
<td>Ulcer heel L (culture: Staphylococcus aureus and Proteus vulgaris)</td>
</tr>
<tr>
<td>16</td>
<td>(M/41)</td>
<td>Numbness in lower legs, absent VS (toes), normal KR, absent AR</td>
<td>No claudication, normal pulsations, mediacalciﬁcation, A/B index 1.08</td>
<td>Amputation of all toes, ulcers lateral and medial side of midfoot R (culture: Staphylococcus aureus); clinically unremarkable Charcot joint R</td>
</tr>
</tbody>
</table>

VS = vibration sense; KR = knee reflex; AR = ankle reflex; and A/B = ankle/branchial blood pressure index.
Indium-111-IgG Scintigraphy

With the bone scan used as a landmark for the osseous structures, 111In-IgG scintigraphy identified six of seven proven osteomyelitis foci. Figure 1 shows scintigraphic images from Patient 7 with histologically proven osteomyelitis.

In all ulcers or gangrenous sites without underlying osteomyelitis (with the exception of Patient 13 who had a completely normal 111In-IgG study), there was mild 111In-IgG accumulation in soft-tissues at the site of the ulcer or gangrene (Table 2, true-negative studies for osteomyelitis). For two patients (nos. 14 and 15), abnormal 111In-IgG accumulation was attributed to the calcaneus, while only a deep soft-tissue infection was present. Figure 2 shows the scintigraphic images of Patient 14. Four patients had Charcot joints, two of them bilaterally. For those patients (nos. 5, 9 and 16) in whom this condition already existed for many months or even years, 111In-IgG scintigraphy was negative. In Patient 16, who had clinically unremarkable Charcot joint, the bone scan was also negative. For Patient 10, who had sustained fractures only 4 wk prior to scintigraphy, 111In-IgG scintigraphy showed accumulation in the osseous structures of the midfoot (Fig. 3). This patient was categorized as false-positive for osteomyelitis. Only one false-negative 111In-IgG scan was observed (Patient 13). This patient had severe arterial angiopathy and histologically proven osteomyelitis of the first toe.

Plain Radiograph

Plain radiographs identified four of seven osteomyelitic foci. False-negative results were obtained in two patients (nos. 5 and 13) with osteomyelitis of a toe and in Patient 7 with osteomyelitis of a metatarsal. Osteomyelitis was correctly ruled out in 15 of 19 lesions. The radiographic findings of three lesions were equivocal for osteomyelitis: osteomyelitis of bilateral Charcot joints could not be ruled out in Patient 9, and in Patient 15 focal demineralization of the calcaneus indicated possible osteomyelitis. In Patient 16, the radiograph indicated involvement of the fifth metatarsal, whereas osteomyelitis could not be established.

Soft-Tissue Culture

In 14 of 16 patients, soft-tissue cultures were obtained. In 12 patients, the cultures showed bacterial growth. Six of these patients had osteomyelitis. In the other six, osteomyelitis could not be proven. Of the two patients with negative cultures, one had osteomyelitis.

The overall sensitivity, specificity and predictive values

### Table 2

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Localization</th>
<th>X-ray</th>
<th>MDP</th>
<th>IgG</th>
<th>Verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>First toe L</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Healing of ulcer</td>
</tr>
<tr>
<td>2</td>
<td>Midfoot R</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Healing of ulcer</td>
</tr>
<tr>
<td>3</td>
<td>Calcaneus L</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Healing of ulcer</td>
</tr>
<tr>
<td>4</td>
<td>Second toe R</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Histology (surgical specimen): osteomyelitis</td>
</tr>
<tr>
<td>5</td>
<td>Midfoot R</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>No evidence of infection (follow-up)</td>
</tr>
<tr>
<td>6</td>
<td>Calcaneus R</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Histology (surgical specimen): osteomyelitis</td>
</tr>
<tr>
<td>7</td>
<td>First toe L</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Superficial ulcer, no bone involvement</td>
</tr>
<tr>
<td>8</td>
<td>Midfoot R</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Charcot joint, no evidence of infection (follow-up)</td>
</tr>
<tr>
<td>9</td>
<td>MTP 1, R</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Histology (surgical specimen): osteomyelitis</td>
</tr>
<tr>
<td>10</td>
<td>Metatarsals 2, R</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Charcot joint, no evidence of infection (follow-up)</td>
</tr>
<tr>
<td>11</td>
<td>Metatarsal 1, L</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Charcot joint, no evidence of infection (follow-up)</td>
</tr>
<tr>
<td>12</td>
<td>Metatarsal 5, L</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Histology (surgical specimen): osteomyelitis</td>
</tr>
<tr>
<td>13</td>
<td>Metatarsal 5, R</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Pressure point, no infection (follow-up)</td>
</tr>
<tr>
<td>14</td>
<td>First toe L</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Charcot joint, no evidence of infection (follow-up)</td>
</tr>
<tr>
<td>15</td>
<td>Calcaneus L</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>Charcot joint, no evidence of infection (follow-up)</td>
</tr>
<tr>
<td>16</td>
<td>Metatarsal 1, R</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Histology (surgical specimen): no osteomyelitis</td>
</tr>
</tbody>
</table>

MTP = metatarsophalangeal joint.
FIGURE 1. Plantar views of $^{99m}$Tc-MDP bone scintigraphy 24 hr p.i. (left panel) and $^{111}$In-IgG scintigraphy 48 hr p.i. (right panel) of Patient 7 (55-year-old female with diabetes mellitus for 42 yr). She had an ulcer at the base of second toe of the right foot that developed after amputation of the toe. Soft-tissue cultures showed growth of Staphylococcus aureus. She also had a pressure point on the base phalanx of the first toe of the left foot that developed after resection of the distal phalanx. The bone scan shows increased activity at the site of both the ulcer (large arrow) and the pressure point (small arrow). Indium-111-IgG scintigraphy correctly identified histologically-proven osteomyelitis in the second metatarsal of the left foot (large arrow) and correctly ruled out infection at the pressure point on the right foot (small arrow).

FIGURE 2. Lateral views of the right foot with $^{99m}$Tc-MDP bone scintigraphy 3 hr p.i. (left panel) and $^{111}$In-IgG scintigraphy 48 hr p.i. (right panel) of Patient 14 (55-yr-old male with diabetes mellitus for 26 yr). He had a deeply penetrating, soft-tissue ulcer of the right heel (soft-tissue culture: Staphylococcus aureus and epidermidis). Both the bone scan and $^{111}$In-IgG scintigraphy show intensely increased activity in the right calcaneus (arrows). The ulcer responded well to antibiotic medication and local treatment and healed without complications in the course of several weeks. Therefore, both studies were categorized as false-positive for osteomyelitis.

for osteomyelitis of the diagnostic procedures are summarized in Table 3.

DISCUSSION

The present study indicates that $^{111}$In-IgG scintigraphy is a potentially useful method for evaluation of possible osteomyelitis of the diabetic foot. Recently, Wegener et al. also indicated the possible use of $^{111}$In-IgG scintigraphy in the diabetic foot, in that they observed that this technique adequately localized the osteomyelitic focus in three patients (18).

By using the bone scan as a landmark for the osseous structures, it is possible in most cases to discriminate osteomyelitis from mere soft-tissue involvement. However, this discrimination is hardly possible on $^{111}$In-IgG scintigraphy alone. When patients suffer from deep soft-tissue ulcers, differentiation between bone and soft-tissue involvement remains difficult, as indicated by patients 14 and 15, who had penetrating hindfoot ulcers. In our study, $^{111}$In-IgG scintigraphy of only one patient (no. 13) was categorized as false-negative for osteomyelitis. The severe arterial angiopathy of this patient may have hampered the supply of $^{111}$In-IgG to the infectious lesion. As reported earlier, recent fractures are pitfalls in the interpretation of $^{111}$In-IgG images (9,10). This was exemplified by the patient with a recent Charcot joint. However, fractures that are several months old pose no problem in the interpretation of the $^{111}$In-IgG scans (9,10). These findings imply that $^{111}$In-IgG scintigraphy appears to be of limited value for the detection of infectious lesions in Charcot joints with recent fractures. This not only applies to $^{111}$In-IgG scintigraphy, but to all scintigraphic techniques, such as $^{67}$Ga and labeled autologous WBC scintigraphy, that are currently used for imaging infectious bone and joint disease (2,5).

The performance of bone scintigraphy in the present study is in agreement with reports in literature (1-5,19,

FIGURE 3. Plantar views of $^{99m}$Tc-MDP bone scintigraphy 24 hr p.i. (left panel) and $^{111}$In-IgG scintigraphy 48 hr p.i. (right panel) of Patient 10 (45-yr-old male with diabetes mellitus for 20 yr). He had a painful Charcot joint of the left foot. He sustained spontaneous fractures in the left foot 4 wk prior to scintigraphy. Both the bone scan and $^{111}$In-IgG scintigraphy show intensely increased activity in the left midfoot (arrows). By wearing specially designed shoes, the patient’s complaints disappeared. This study is an example of recent fractures inducing false-positive bone scan and $^{111}$In-IgG studies.
TABLE 3
Summary of the Performance of Various Techniques for Detection of Osteomyelitis

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>TP</th>
<th>TN</th>
<th>FN</th>
<th>FP</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft-tissue culture</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>86%</td>
<td>14%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Plain radiograph</td>
<td>26</td>
<td>4</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>57%</td>
<td>79%</td>
<td>50%</td>
<td>84%</td>
</tr>
<tr>
<td>99mTc-MDP</td>
<td>26</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>100%</td>
<td>0%</td>
<td>27%</td>
<td>—</td>
</tr>
<tr>
<td>111In-IgG</td>
<td>26</td>
<td>6</td>
<td>16</td>
<td>1</td>
<td>3</td>
<td>86%</td>
<td>84%</td>
<td>67%</td>
<td>94%</td>
</tr>
</tbody>
</table>

TP = true-positive; TN = true-negative; FN = false-negative; FP = false-positive; PPV = positive predictive value; and NPV = negative predictive value.

20). We also observed superb sensitivity. Specificity was extremely low in our study, since all clinically suspect osteomyelitic foci showed increased 99mTc-MDP uptake.

The accuracy of plain radiographs also confirms previous reports (1,4,7,19,20). Initially a plain radiograph may show only soft-tissue swelling, periostal reaction or cortical irregularities, but these findings are nonspecific. Diagnostic findings only become apparent after a certain degree of bone loss. Diabetic osteopathy may significantly interfere with interpretation of the radiographs.

With regard to other scintigraphic techniques for imaging infection, 67Ga is the least suitable for this group of patients, mainly due to accumulation in areas of increased bone turnover resulting in a relatively low specificity (2,4,5).

Several authors have reported good results with 111In-labeled WBCs (2,6,7,21). Maurer et al. observed a clearly increased specificity of 111In-labeled WBC scintigraphy in comparison to the bone scan (21). Schauwecker et al. indicated the usefulness of dual-isotope imaging using a 99mTc-labeled bone scanning agent and 111In-labeled WBC (6). They were able to discriminate bone from soft-tissue infection in 89% of their patients. In a series of 77 patients, Keenan et al. observed 100% sensitivity and 79% specificity for osteomyelitis (7). In contrast to Schauwecker et al., they felt that little benefit was obtained from bone scans (6,7). When compared to 111In-IgG preparations, the main drawback for widespread use of labeled WBCs is the relatively complicated and time-consuming cell labeling. Isolating and labeling leukocytes takes at least 3 hr. Moreover, careful handling of the potentially infectious blood is necessary to avoid infection of both the staff and other patients. In contrast, the IgG-DTPA is readily available as a sterile, pyrogen-free kit for convenient one-step labeling. Indium-111-IgG is ready for injection within half an hour.

To our knowledge, scarce data are available on detecting diabetic foot infections with other new scintigraphic techniques, such as 99mTc-labeled IgG and labeled monoclonal antigranulocyte antibodies. Weidlich et al. observed 90% sensitivity and 90% specificity for osteomyelitis in a group of 20 diabetic patients using the murine monoclonal antigranulocyte antibody BW 250/183 (22).

Magnetic resonance imaging (MRI) could lead to improvement in the management of diabetic foot complications. First reports indicate excellent sensitivity. Yuh et al. observed 100% sensitivity and only two false-positive results (specificity 89%) in a group of 24 patients (20). However it appears that MRI also shows false-positive results in osteoarthropathy of recent onset (2). Seibold et al. found a similar sensitivity of MRI and 111In-labeled WBC imaging in diabetic feet (2).

It is not possible to estimate the probability of osteomyelitis on the basis of culturing soft-tissue specimens. Our results revealed that 50% of patients with positive soft-tissue cultures actually had osteomyelitis. Moreover, one of the two patients with negative soft-tissue cultures had osteomyelitis.

In conclusion, it has been shown that 111In-IgG scintigraphy appears promising for evaluation of suspected diabetic foot infections. The presence and the extent of possible bone involvement can be reliably assessed. Ulcers penetrating deeply in the soft-tissues, but not in bone, may cause false-positive results for osteomyelitis. The conventional bone scan can be useful in determining the likelihood of osteomyelitis, since a normal bone scan virtually rules out osteomyelitis. Moreover, a bone scan is essential for localizing osseous structures of the foot when 111In-IgG scintigraphy is subsequently performed.

REFERENCES

9. Oyen WJG, Claessens RAMJ, van Horn JR, van der Meer JWM, Corstens
True statements regarding the use of $^{67}$Ga scintigraphy in evaluation of patients with lung cancer include:

26. Gallium-$^{67}$ localizes in pulmonary tissues primarily within the first 6 hr after administration.

27. Gallium-$^{67}$ uptake at sites of inflammation is almost always due to the presence of lactoferrin-containing polymorphonuclear leukocytes.

28. The primary serum transport protein for $^{67}$Ga is albumin.

29. Large extracellular fluid compartments and increased capillary permeability are both important factors contributing to the localization of $^{67}$Ga.

True statements regarding technical aspects of $^{67}$Ga scintigraphy of the chest include:

30. Sensitivity for detection of malignant pulmonary lesions falls when the size of the lesions is less than 1.5 cm.

31. Twenty-four-hour images are optimal for quantitative assessments of pulmonary disease activity.

32. Factors improving sensitivity of $^{67}$Ga imaging for tumor screening include all of the following: triple peak acquisition, 72-hr imaging, 10-mCi (370-MBq) dose, and tomography.

33. Bronchoscopy within the 24-hr period prior to $^{67}$Ga administration frequently causes false-positive scintigrams.

34. Gallium-$^{67}$ scans are less sensitive for detection of sites of pulmonary neoplasia occurring near the mediastinum than those involving peripheral lung.

True statements regarding the use of $^{67}$Ga scintigraphy in evaluation of patients with lung cancer include:

35. Gallium scintigraphy is positive in 85%-95% of patients with carcinoma of the lung.

36. Chest radiography, either alone or in combination with laminography or computed tomography, is the procedure of choice in lung cancer screening.

37. If a peripheral, primary lung cancer localizes gallium but the mediastinum is free of uptake, there is still better than an 80% likelihood that the mediastinal lymph nodes will be positive by mediastinoscopy.

38. Uptake of $^{67}$Ga by primary lung cancers is correlated with the frequency of metastasis and survival.

39. If the primary tumor accumulates $^{67}$Ga, the likelihood that an extrapulmonary focus of gallium uptake in a metastasis is less than 70%.

(continued from page 1303)

**SELF-STUDY TEST**

**Pulmonary Nuclear Medicine**

True statements concerning evaluation of regional ventilation by $^{133}$Xe scintigraphy include:

15. Regions of compromised ventilation are indicated either by slow tracer entry noted on washin images or by delayed clearance on washout images.

16. Tracer concentration and chest wall thickness affect count rate during xenon washout studies, but these factors have no effect on regional xenon clearance rates.

17. The time required to clear xenon from the lungs is largely unaffected by local alveolar volume and air flow.

18. Depth and frequency of respiration affect global rates of tracer clearance but have little influence on relative clearance patterns from individual lung regions.

19. Alveolar compliance and airways resistance are important determinants of the rate of regional xenon clearance.

A 76-yr-old man with a 60 pack-yr smoking history presents with a 3-cm right lower lobe mass. Prior to right pneumectomy an 80% likelihood that the mediastinal lymph nodes will be positive by mediastinoscopy.

True statements concerning the mechanisms of $^{67}$Ga uptake in pulmonary disease include:

25. The gallium ion is similar to the ferric ion in atomic charge and radius.