Infectious Imaging with Indium-111-Labeled Nonspecific Polyclonal Human Immunoglobulin

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Nonspecific polyclonal immunoglobulin (IgG), prepared from pooled human serum gamma globulin and labeled with ^{111}In has been reported to be equivalent to antigen-specific antibody in the detection of focal infection or inflammation during the first 24 hr after injection. We describe our experience in a Phase II clinical study using ^{111}In-IgG in 15 patients (8 males, 7 females) ranging from 26 to 80 (mean = 50) yr of age with suspected focal infection/inflammation. Pathologic confirmation was obtained in 5/15 cases. A combination of clinical course, laboratory results, and other imaging procedures were used to categorize the other 10 patients. One possible false-negative involved a presumed aspiration pneumonia in a patient with a history of aspiration, bibasilar infiltrates on chest film, and no other identified source of infection. Otherwise, there were 10 confirmed positives, 4 confirmed negatives, and no false-positives. Our findings confirm earlier reports that ^{111}In-IgG may be a superior imaging agent for infection/inflammation with practical advantages over ^{67}Ga-citrate and ^{111}In-labeled leukocytes.

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Functional radionuclide imaging techniques play an important role in the detection of infection/inflammation early in its course, before the occurrence of extensive tissue damage that can be visualized using anatomic radiologic imaging modalities (CT, US, MRI). Radionuclide scans are especially useful in localizing the site of infection when the disease location is unknown as in cases of fever of unknown origin (FUO), with non-focal disease such as peritonitis, and when distorted anatomy is present as in the post-surgical patient (*1–7*).

Gallium-67-citrate and ^{111}In-labeled leukocytes (^{111}In-WBCs) are the principle scintigraphic agents employed clinically for imaging infection. Inherent disadvantages associated with their preparation or application otherwise limit their effectiveness (*1–7*). The normal route of excretion of ^{67}Ga into the bowel lumen compromises its sensitivity and specificity for the detection of abdominal infection. Indium-111-WBCs require phlebotomy, a prolonged (2-hr) complicated laboratory preparation procedure, and a small administered dose (500 μCi), due to unfavorable dosimetry thus limiting image resolution and consequently localization due to low photon flux. These drawbacks have not been completely eliminated by the development of alternative radiopharmaceuticals such as ^{99m}Tc-labeled leukocytes (*8,9*) or radiolabeled monoclonal antibodies specific for leukocyte surface antigens (*10,11*).

Indium-111-IgG is a new infectious imaging agent consisting of ^{111}In-labeled nonspecific polyclonal immunoglobulin (IgG) prepared from pooled human serum gamma globulin. Indium-111-IgG is available in simple kit form, is administered as a single intravenous injection (does not require phlebotomy or complex laboratory preparation), is not excreted in the intestine, and may be administered in doses up to 2.4 mCi due to favorable dosimetry. Basic studies (*12,13*) and early clinical results (*14–16*) indicate that ^{111}In-IgG may be a superior imaging agent with practical advantages over ^{67}Ga and ^{111}In-WBCs. In this report, we describe our experience with ^{111}In-IgG in a variety of patients with suspected focal infection.

MATERIALS AND METHODS

Patient Population

Patients were recruited only if there was a strong suspicion of a focal infection or inflammation. A total of 15 patients were studied, 8 males and 7 females. Subjects ranged in age from 26 to 80 yr with a mean of 50 yr.

Inclusionary criteria required that the patient be >21 yr of age and have one of the following: (1) a positive culture, (2) a localizing feature plus fever, or (3) a localizing feature plus focal radiologic abnormality. Acceptable localizing features included: (1) localized pain, (2) abdominal or pelvic pain (not of diarrheal origin) >3 days in duration, or (3) the presence of a native aortic aneurysm, vascular or orthopedic prosthesis. Fever was defined as a daily temperature spike >100.5°F lasting for >3 days. Radiologic examinations were done within one week of study initiation. These included conventional radiographs, ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT), and triple-phase bone scans using ^{99m}Tc-labeled methylene diphosphonate (^{99m}Tc-MDP).

Exclusionary criteria included: (1) hypotension, (2) shock or medical instability, (3) uremia (bun > 50 or serum creatinine > 2.5 mg/dl), (4) recent exposure to an experimental drug/device

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<30 days prior to admission in the study, (5) a history of agammaglobulinemia, hypogammaglobulinemia, or selective IgA deficiency, or (6) a history of previous severe systemic reaction to gamma globulin products. Women of childbearing age required a negative serum pregnancy test, an effective method of contraception prior to and during the study, and could not be lactating. All patients participating in the study signed an institutionally approved consent form.

Radiopharmaceutical

Indium-111-chloride (Amersham, Arlington Heights, IL) was supplied in a sterile, pyrogen-free form without radionuclide impurities (carrier-free; <0.1% ^{114m}In and <0.1% ^{65}Zn). Since it was used within 3 days of receipt, these minor contaminants remained insignificant. The pooled collection of human serum globulins used in this study is commercially available from Cutter Biological as Gamimune™. The particular immunoglobulin preparation employed was obtained in sterile, pyrogen-free kit form from the R.W. Johnson Pharmaceutical Research Institute (Spring House, PA.; formerly Ortho-Biotech Imaging Products). Each kit consisted of two 5 ml vials that were refrigerated until use. One vial contained 0.25 M sodium citrate buffer while the second vial contained DTPA-IgG complex prepared via the carboxy-carbonic anhydrase method originally described by Krejcarek and Tucker (*17*) as modified by Khaw et al. (*18*). The DTPA-IgG complex was supplied in 2.3 ml of 0.01M phosphate buffered saline with pH 7.0–7.4.

Using aseptic technique, after standing at room temperature for 10 min, 0.5 ml of the sodium citrate buffer was injected into the vial containing DTPA-IgG, followed by 2 mCi of the ^{111}In-chloride. The contents were gently mixed and allowed to stand at room temperature for 15 min. The total activity was checked in a radionuclide dose calibrator. Radiochemical purity testing was performed using thin-layer chromatography and required >90% labeling efficiency within 1 hr of preparation. The patient dose was then withdrawn through a Millex-GV filter and checked to be free of cloudiness, precipitates or particulates. In all cases, the radiopharmaceutical was injected within 1 hr of preparation.

Protocol

Blood chemistries, hematology, urinalysis, and a physical exam were performed both prior to and following each study. Each patient was closely observed following the intravenous injection of the radiopharmaceutical and vital signs were obtained at regular intervals.

Whole-body images were obtained at approximately 6 and 24 hr following injection; occasionally, additional images were obtained at 48 or 72 hr postinjection. Patients were imaged using a large field of view gamma camera, a medium-energy parallel-hole collimator, and 20% energy windows about both 173 and 247 keV photopeaks of ^{111}In. Approximately 300,000–500,000 counts were collected per image. Analog images were obtained as well as digital images using an interface to a Star II™ GE computer. To avoid shinethrough artifacts from ^{99m}Tc, bone scans were obtained either after ^{111}In imaging or at least 2 days in advance.

Image Interpretation/Confirmation

Scans were interpreted as being abnormal if there was any abnormal focal activity. Although categories such as possible and probable abnormality were allowed initially, in practice, we were able to be more definitive and interpret each scan as being either normal (no apparent abnormality) or abnormal without resorting to these qualifiers. Both analog and digital images were reviewed before arriving at an interpretation. In most cases, the scans were reviewed by three nuclear medicine physicians who independently arrived at a conclusion. Occasional disagreement was resolved by discussion. If pathology was obtained within 1 wk of the study period, these results were used to confirm scan interpretation. Otherwise, confirmation was obtained by a combination of clinical course, laboratory results and other imaging studies.

RESULTS

All 15 studies were conducted without event. One kit was discarded when radiolabeling only achieved 87% labeling efficiency; otherwise, radiopharmaceutical preparation was unremarkable. There were no side effects due to administration of the radiopharmaceutical. Table 1 summarizes study results, including from other imaging modalities, pathology confirmation if available, and final study interpretation. Indium-111-IgG imaging results were

TABLE 1
Study Results in 15 Patients with Suspected Infection

Patient no.	Age	Sex	Site	Indication	IgG interpretation	Correlation	Pathology	Final
1	64	M	Bone	TKA: Inf vs. Loose	Inf Prosth	BS: Pos for Inf	No	TP
2	70	F	Bone	THA: Inf vs. Loose	Loosening	BS: Neg for Inf	Neg	TN
3	50	M	Bone	THA: Inf vs. Loose	Loosening	BS: Neg for Inf	Neg	TN
4	28	F	Bone	Diabetic Ft Dz	Osteo	BS: Pos for Osteo	No	TP
5	52	M	Bone	Diabetic Ft Dz	Osteo	BS: Pos for Osteo	No	TP
6	80	F	Bone	Diabetic Ft Dz	Osteo	BS: Pos for Osteo	No	TP
7	34	M	Bone	Recur Hip Inf	Resid Inflmn	CT: Osteo/sinus tract	No	TP
8	48	M	Bone	h/o Fem Osteo	Osteo	BS: Pos for Osteo	No	TP
9	53	F	Bone	Acute ankle pain	Osteo	BS: Pos for Osteo	No	TP
10	32	F	Pelvis	r/o recur TOA	Resid Inflmn	CT/US: Adnexal abcess	No	TP
11	40	F	Abd	r/o Surg Abcess	Neg Scan	Asp CT: Hematoma	Neg	TN
12	74	M	Abd	Psoas Abcess	Extensive Inf	CT/XR: Abcess, ext to leg	Pos	TP
13	26	F	Abd	Crohn's Dz, FUO	Nonactive Dz	CT/E. lap: Neg Inflm	Neg	TN
14	35	M	Vasc	r/o Septic DVT	ST Inflmn	BS: Neg for Osteo	No	TP
15	69	M	Lung	r/o Pneumonia	Neg Scan	CXR: Asp Pneumonia	No	FN

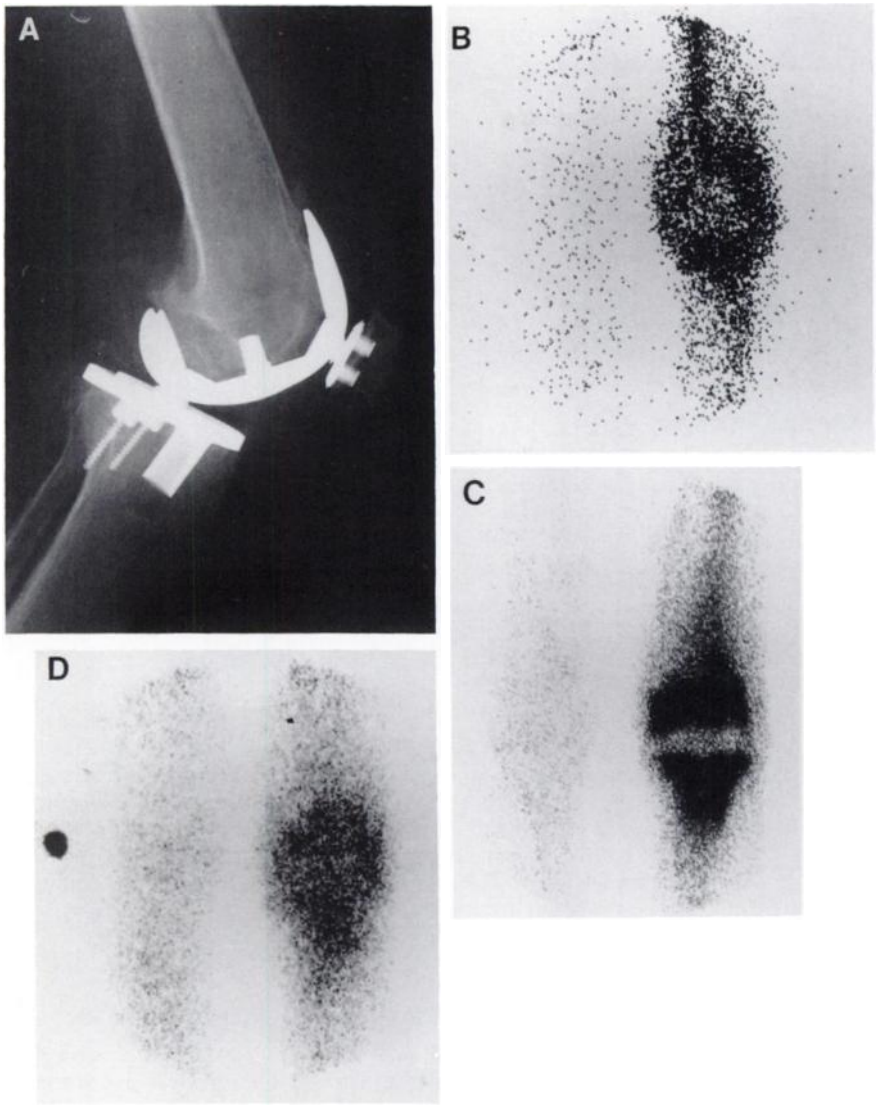

FIGURE 1. Patient 4, a 64-yr-old male diabetic. Indium-111-IgG and 3PBS demonstrated unresolved left TKA infection following arthroscopic debridement and 6-wk intravenous vancomycin. Two weeks later, the prosthesis was removed with intraoperative cultures positive for coagulase negative Staphylococcus. (A) Plain radiograph. (B) 3PBS blood flow activity. (C) 3PBS 3-hr image. (D) Indium-111-IgG 24-hr image.

confirmed by pathology in five patients, with one positive and four negative results obtained. A combination of clinical course, laboratory results and other imaging procedures were used to provide confirmation in the other ten patients.

Nine patients had suspected osteomyelitis, mostly involving chronic or predisposing conditions such as a knee or hip prosthesis (Patients 1–3), diabetic foot disease (Patients 4–6), or recurrent infection in the hip (Patient 7) or femur (Patient 8). Only in Patient 9 was acute osteomyelitis suspected without trauma or other predisposing complication. The seven other patients included suspected pelvic inflammatory disease (Patient 10), suspected postsurgical abcesses (Patients 11 and 12), Crohn's disease with suspected infection (Patient 13), suspected infected deep venous thrombosis in an intravenous drug abuser (Patient 14), and suspected aspiration pneumonia in a long-term care patient (No. 15).

Patients 1–9 with suspected osteomyelitis included seven true-positives and two true-negatives. Triple-phase bone scintigraphy was used in most cases, while CT demonstrated extensive destruction in Patient 7 with recurrent hip infection. Representative positive scan results from Patients 1, 7 and 8 are shown in Figures 1–3. Results in Patients 2 and 3 were consistent with noninfectious prosthesis loosening. All three patients with diabetic foot disease (Patients 4–6) had positive ^{111}In-IgG scan findings that matched focal triple-phase bone scan abnormalities in the distal foot. Triple-phase bone scan abnormalities themselves are nonspecific in this group and bone cultures were not obtained near the time of the ^{111}In-IgG study. Nonetheless, by subsequent hospitalization course, including an amputation in Patient 5, all three patients were clinically diagnosed as having probable osteomyelitis at the time of the ^{111}In-IgG scan. In Patient 9 with no trauma or prior bone complications, focal triple-phase bone scan findings at the ankle were felt to be specific for acute osteomyelitis and in keeping with clinical symptomatology. Although images obtained at 6 hr were always abnormal in these positive studies, the 24-hr images often al-

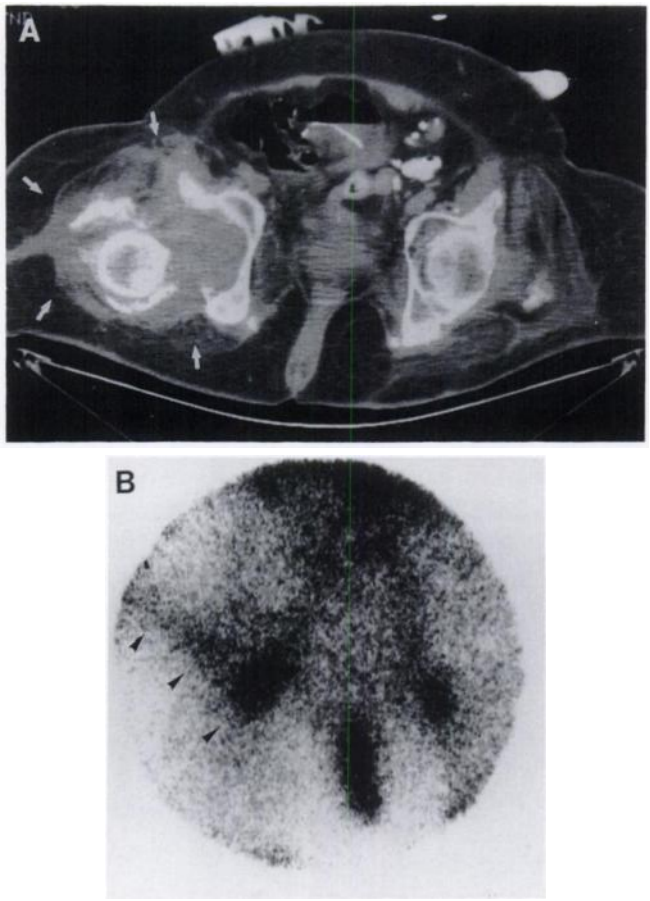

FIGURE 2. Patient 7, a 34-yr-old male paraplegic. Right hip surgery with recurrent infections, following surgical drainage and 6 wk intravenous antibiotics for *S. aureus*. Indium-111-IgG demonstrated residual inflammation in clinically stable patient. (A) CT with right hip destruction and sinus tract (arrows). (B) Indium-111-IgG 6-hr image, including sinus tract activity (arrowheads).

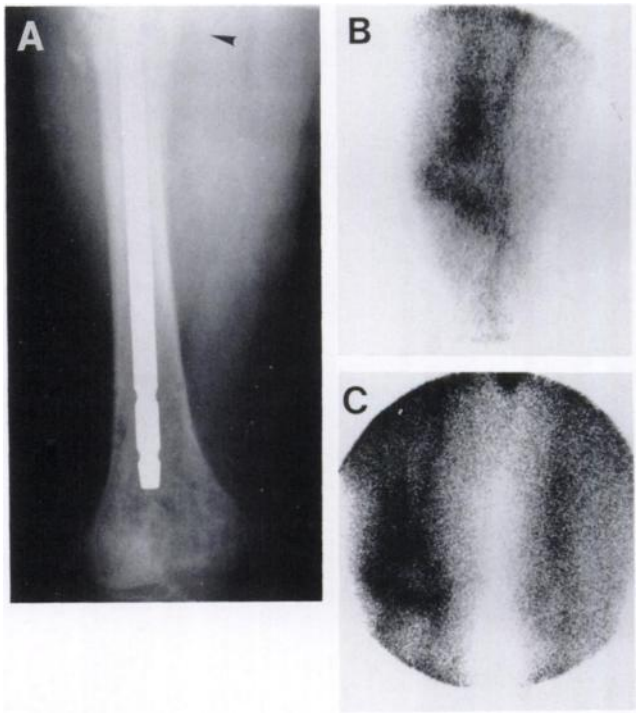

FIGURE 3. Patient 8, a 48-yr-old male. Recurrent infections of traumatic right femoral fracture, now with fever and localized pain. Indium-111-IgG and 3PBS consistent with infection at distal intramedullary rod. Patient responded well to antibiotic treatment with negative intraoperative cultures when the rod was removed 1 mo later. (A) Plain radiograph with probable proximal nonunion (arrowhead). (B) Indium-111-IgG 24-hr image. (C) 3PBS blood-pool image.

lowed more precise localization with increased confidence of abnormality. This was particularly important in the distal extremities in order to distinguish among the many small bones and joints.

In Patients 10–13 with suspected abdominal/pelvic infections, there were two true-positives and two true-negatives. Positive findings from Patients 10 and 12 are presented in Figures 4 and 5, respectively. Diagnostic images were obtained by 6 hr in both cases, with little additional information at 24 hr. Patient 11 had what proved to be a postoperative sterile subrectus sheath hematoma percutaneously aspirated under CT. For Patient 13 with Crohn's disease and fevers, CT and exploratory laparotomy both failed to reveal any active inflammation.

For Patient 14 with a suspected septic DVT, there was no evidence of osteomyelitis by triple-phase bone scan. Although no focal ^{111}In-IgG activity was seen at the thrombus, the scan results were interpreted as a true-positive finding because there was a mild diffuse pattern throughout the surrounding soft tissues, consistent with an inflammatory reaction. In this case, the diffuse pattern seen at 6 hr remained similar in appearance at 24 hr.

In Patient 15 with a suspected aspiration pneumonia, the ^{111}In-IgG scan was unremarkable, including the thorax. This result was considered as false-negative because there were bibasilar infiltrates on chest film, the patient had a history of aspiration, and no other source of infection was identified.

DISCUSSION

Our experience indicates that ^{111}In-IgG is a safe and useful imaging agent for the detection of focal infection/inflammation. With its good contrast and uptake in inflammatory regions, lesion sites in both soft and bony tissues were well visualized by 24 hr and usually earlier by 6 hr. In ten patients with infection, ^{111}In-IgG imaging correctly identified the site of involvement. In four patients without infection, ^{111}In-IgG imaging found no abnormalities. Only in one patient did ^{111}In-IgG imaging apparently fail to reveal an abnormality, and this conclusion is based largely on circumstantial evidence of an aspiration pneumonia. Summarizing our study of 15 patients, then, there were ten confirmed positives, four confirmed negatives, one false-negative, and no false-positives.

The potential usefulness of nonspecific IgG imaging

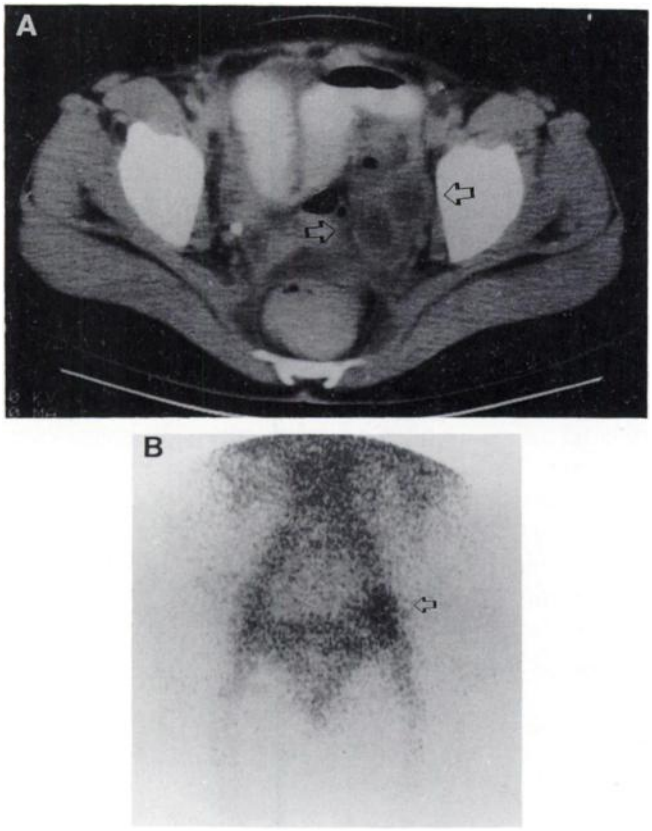

FIGURE 4. Patient 10, a 32-yr-old female. Recurrent PID. Left lower quadrant pain responded immediately to intravenous antibiotics. Indium-111-IgG revealed residual infection or inflammation. Following continued improvement, patient was discharged. (A) Pelvic CT with complex left adnexal mass (arrows). (B) Indium-111-IgG 6-hr image with left ovarian activity (arrow).

agents was initially realized in animal experiments as focal bacterial infections were being imaged with radiolabeled IgG (*12*). After 24 hr, lesion uptake of monoclonal IgG specific for bacterial antigens exceeded that of control nonspecific IgG. However, during the first 24 hr, lesion uptake of nonspecific and specific IgGs was equivalent, indicating an effective and nonspecific mechanism of early entrapment. Similar experiments with sterile lesions demonstrated that nonspecific IgG effectively localized inflammatory sites, infectious or otherwise. Other animal studies demonstrated that radiolabeled nonspecific human IgG was superior to ^{99m}Tc-labeled albumen and ^{67}Ga during the first 24 hr, with better percent uptake and higher target-to-background ratios in experimentally induced focal infections (*13*).

In the first clinical studies using ^{111}In-IgG, Fischman et al. (*14*) reported a 92% sensitivity and 95% specificity in a series of 84 patients with a variety of suspected lesions in the abdomen, pelvis, lungs, bones, joints, or in vascular grafts. In a larger series of 128 patients with a similar variety of suspected infections, Rubin et al. (*15*) later reported a sensitivity of 91% and specificity of 100%. Recently, Oyen et al. (*16*) reported that ^{111}In-IgG correctly identified all confirmed sites of infection or inflammation in 25 patients with suspected musculoskeletal infections.

The distribution of ^{111}In-IgG does not appear to be adversely affected by antibiotics, or other medications. One potential disadvantage of using ^{111}In-IgG includes its altered physiologic distribution in cases of uremia; since uremic patients were excluded from the study we cannot ascertain if this is indeed a serious limitation (*15*). The natural physiologic distribution of ^{111}In-IgG may obscure lesions in the liver, spleen, and kidneys, resulting in false-negative scans. Although the splenic uptake of ^{111}In-IgG appears less than that with ^{111}In-WBCs, false-positives could still arise in rare cases of ectopia. Indium-111 Igg also exhibits greater intravascular activity, with an approximate circulation half-life of 24 hr (*19*) compared to 7 hr for ^{111}In-WBCs (*6*). These potential distribution limitations did not seem to be a serious problem in our study. Unlike ^{67}Ga, no significant normal bowel activity is seen, so that multiple delayed imaging sessions may be avoided.

Indium-111-IgG is available in a sterile kit form simply prepared by the addition of ^{111}In-chloride. Unlike ^{111}In-WBCs, phlebotomy and a laborious preparation are not required. These considerations are particularly important in community hospitals where necessary laboratory facilities may not be available for cell labeling, in patients with poor venous access, and especially in pediatrics where an adequate blood sample may be difficult to obtain.

Indium-111-IgG dosimetry estimates, obtained from adult volunteers, determine the target organ to be the liver with 1.42 rads/mCi and include red marrow, 0.98 rads/mCi; testes, 1.23 rads/mCi; ovaries, 0.53 rads/mCi; kidneys, 0.73 rads/mCi; and spleen, 0.75 rads/mCi (*19*). These estimates compare favorably, in particular, avoiding the substantial splenic dose delivered by ^{111}In-WBCs and avoiding entirely the intense irradiation of lymphocytes that occurs during ^{111}In-WBC in vitro labeling (*6, 20*). As such, 2.4 mCis of ^{111}In-IgG may be given in adults, compared to only 0.5 mCis of ^{111}In-WBCs. This increased dose shortens imaging time, decreases the chances of patient motion and therefore leads to a better study result. In addition, the greater photon flux permits higher count images to be obtained in reasonably short imaging time with resultant improvement in image quality.

Except for enhanced tissue perfusion and increased vascular permeability expected in regions of inflammation, the mechanism of ^{111}In-IgG localization is unknown. Fc fragments show uptake comparable to intact IgG and much greater than that of Fab fragments (*21*). However, localization does not appear to be due to increased leukocyte Fc receptor activity (*22*). The Fc portion of IgG may undergo configurational changes or extracellular binding that slows egress from inflammatory sites, but this possibility remains speculative.

Although ^{111}In-IgG may offer advantages for imaging infections, possible limitations of this agent deserve mention. A sterile inflammation may appear indistinguishable

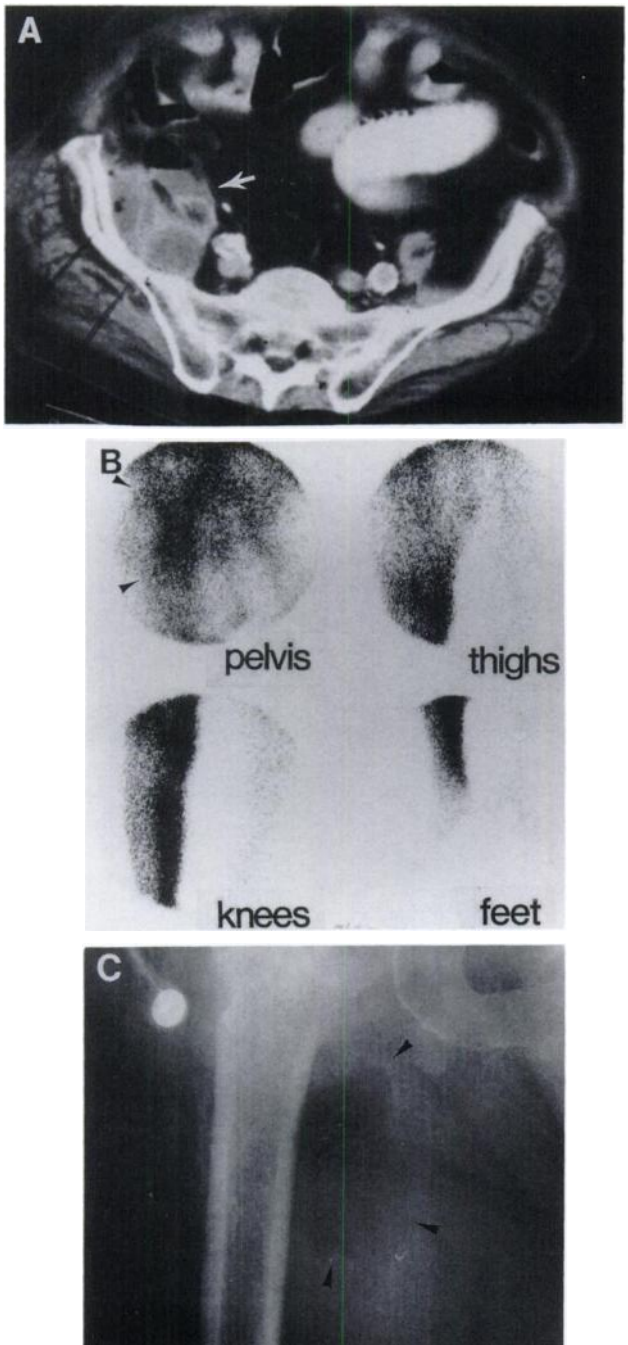

FIGURE 5. Patient 12, a 74-yr-old steroid-dependent male. Right psoas abcess percutaneously drained and positive for bowel flora. Progressive deterioration on multiple intravenous antibiotics. Indium-111-IgG demonstrated abscess and also unexpected activity throughout acutely swollen right lower extremity. Surgical exploration found extensive gangrenous necrosis. Massive debridement was attempted, but overwhelming septic shock followed. (A) CT with psoas abcess (arrow). (B) Indium-111-IgG 24-hr images with abcess site (arrowheads) and lower extremity activity. (C) Radiograph with soft-tissue gas (arrowheads).

from an active infection, since ^{111}In-IgG exhibits nonspecific uptake in any inflammatory region. By study design, only relatively advanced cases of focal disease were considered here. The sensitivity of ^{111}In-IgG for early disease and for disease of limited extent remains to be determined. Since many lesions were detected 6 hr after injection, infectious imaging might be feasible using ^{99m}Tc rather than ^{111}In. Initial studies of ^{99m}Tc-labeled polyclonal human immunoglobulin in mice have been promising (*23*). However, because of the relatively slow clearance of polyclonal antibodies, other infectious agents will likely be required for earlier definitive images. Rapid detection within 1 hr postinjection has been reported in humans with ^{99m}Tc-labeled nanocolloids (*24*) and recently in rats with ^{111}In-labeled chemotactic peptide analogs (*25*).

In summary, ^{111}In-IgG is an easily prepared agent that appears efficacious in the detection of focal infection/inflammation and offers many practical advantages over ^{67}Ga and ^{111}In-WBCs. The small number of patients studied here naturally limits the strength of our conclusions. More definitive results must await further experience with ^{111}In-IgG, including prospective studies and direct comparison with ^{111}In-WBCs.

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