Clinical Utility of Indium 111–Labeled White Blood Cell Scintigraphy for Evaluation of Suspected Infection

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Background. We sought to characterize the clinical utility of indium 111 (^{111}In)–labeled white blood cell (WBC) scans by indication, to identify patient populations who might benefit most from this imaging modality.

Methods. Medical records for all patients who underwent ^{111}In-labeled WBC scans at our tertiary referral center from 2005 to 2011 were reviewed. Scan indication, results, and final diagnosis were assessed independently by 2 infectious disease physicians. Reviewers also categorized the clinical utility of each scan as helpful vs not helpful with diagnosis and/or management according to prespecified criteria. Cases for which clinical utility could not be determined were excluded from the utility assessment.

Results. One hundred thirty-seven scans were included in this analysis; clinical utility could be determined in 132 (96%) cases. The annual number of scans decreased throughout the study period, from 26 in 2005 to 13 in 2011. Forty-one (30%) scans were positive, and 85 (62%) patients were ultimately determined to have an infection. Of the evaluable scans, 63 (48%) scans were deemed clinically useful. Clinical utility varied by scan indication: ^{111}In-labeled WBC scans were more helpful for indications of osteomyelitis (35/50, 70% useful) or vascular access infection (10/15, 67% useful), and less helpful for evaluation of fever of unknown origin (12/35, 34% useful).

Conclusions. ^{111}In-labeled WBC scans were useful for patient care less than half of the time at our center. Targeted ordering of these scans for indications in which they have greater utility, such as suspected osteomyelitis and vascular access infections, may optimize test utilization.

Keywords. leukocyte scintigraphy; nuclear imaging; prosthetic graft infection; osteomyelitis.

Indium 111 (^{111}In)–labeled white blood cell (WBC) scintigraphy is an imaging modality that is used in the diagnostic evaluation of occult infections when other imaging modalities are either contraindicated or uninformative. Labeled leukocytes migrate to and accumulate at sites of inflammation, which are then visualized on nuclear imaging. ^{111}In-labeled WBC scans detect localized inflammation, but do not clearly distinguish between infectious and noninfectious inflammatory processes [1]. ^{111}In-labeled WBC scans have been used in the diagnostic evaluation of fever of unknown origin (FUO) [2–4], prosthetic joint infections [3], vascular graft infections [5–7], and osteomyelitis [3, 8].

Test performance characteristics are traditionally reported in terms of sensitivity, specificity, and overall diagnostic accuracy. Reported sensitivity of ^{111}In-labeled WBC scans for the diagnosis of infectious conditions ranged from 60% to 100% and specificity ranged from 69% to 92% in several series (Table 1) [2–5, 7–9]. Furthermore, the sensitivity of ^{111}In-labeled WBC scans for detection of chronic infections is reported to be similar to that for detection of acute infections [10].

^{111}In scans are often used as adjunctive tools in cases of diagnostic uncertainty. Providers look to the results of ^{111}In scans to inform clinical decision making. However, Wanahita et al postulated that, despite sensitivity and specificity >80%, ^{111}In-labeled WBC scans are not accurate enough to meaningfully impact clinical care in cases of difficult clinical decisions, such as whether or

Received 15 August 2014; accepted 2 September 2014.

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DOI: 10.1093/ofid/ofu089

Table 1. Selected Prior Studies of Test Characteristics of Indium 111–Labeled White Blood Cell Scans for Diagnosis of Infections

Reference	Indication	Methodology	Sensitivity	Specificity
Seshadri et al (2008) [2]	FUO (n = 54)	Retrospective Gold standard: overall clinical assessment at 6 months	0.60	0.71
Kjaer et al (2002) [4]	FUO (n = 19)	Prospective Gold standard: overall clinical assessment	0.71	0.92
Wanahita et al (2007) [3]	Bone/joint infection (n = 145) Non-specific (n = 39)	Retrospective Gold standard: overall clinical assessment at 6 months	0.83 0.81	0.90 0.87
Schauwecker (1989) [8]	Osteomyelitis (n = 485)	Retrospective Gold standard: overall clinical assessment	0.81	0.89
Newman (1991) [9]	Osteomyelitis/DFU (n = 41)	Prospective Gold standard: bone biopsy and culture	0.89	0.69
Brunner (1986) [7]	Vascular graft infection (n = 70)	Retrospective Gold standard: operative/autopsy findings	1.00	0.85
Shahidi (2007) [5]	Vascular graft infection (n = 53)	Retrospective Gold standard: operative findings, overall clinical assessment	0.73	0.87

Abbreviations: DFU, diabetic foot ulcer; FUO, fever of unknown origin.

not to perform a revision arthroplasty on a suspected prosthetic joint infection [3]. This assertion warrants further evaluation. In the current era where increased emphasis is placed on decreasing waste and increasing value in clinical medicine, an assessment of the clinical utility of diagnostic tests must be considered.

The purpose of this investigation was to evaluate the historical use of ^{111}In-labeled WBC scans, and to assess the frequency with which ^{111}In-labeled WBC scans significantly impacted clinical care at our tertiary care center.

METHODS

All patients who underwent ^{111}In-labeled WBC scans at Duke University Hospital between January 1, 2005 and December 31, 2011 were identified via the Duke Enterprise Data Unified Content Explorer (DEDUCE), a tool utilized at our center to query multiple databases containing clinical data [11]. Patient demographic information, the clinical setting in which the scan was obtained (ie, outpatient vs inpatient), and the ordering provider and/or service were obtained utilizing this query tool. Two infectious disease physicians independently reviewed the electronic medical records of all patients who underwent ^{111}In-labeled WBC scans and obtained the following additional data elements: clinical indication for scan, scan result, diagnosis, and scan utility.

Clinical indications for scans were determined by review of provider documentation at the time the scan was ordered. Indications were categorized as one of the following: FUO, suspected osteomyelitis, suspected prosthetic device infection (eg, prosthetic joint, pacemaker), suspected vascular access infection (eg, dialysis graft), known other infection (eg, persistent staphylococcal bacteremia), or other.

Scan result was determined from the attending radiology report. The result was defined as positive if the radiology report described a focal, nonphysiologic change (generally a focal increase) in ^{111}In uptake that was subsequently found to be a site of infection. A scan result was defined as negative if the radiology report described no focal change in ^{111}In uptake, or if a focal change was found that did not correspond to the site of a subsequently confirmed infection. A scan result was defined as indeterminate if nonspecific changes in ^{111}In uptake were described, or if it was otherwise not possible to ascertain from the radiology report whether a focal increase in ^{111}In uptake was present, suggestive of infection.

The final diagnosis was determined based on review of the comprehensive electronic medical record. Final diagnoses were categorized as infectious if the patient had clinical evidence of infection supported by appropriate microbiologic and pathologic data, noninfectious if an alternate diagnosis was made based on a combination of clinical, laboratory, and radiographic data (including, eg, follow-up with no evidence of emergent infection if antimicrobial therapy was not used), or indeterminate if a clear diagnosis was not evident after a review of all available medical records. Similar methodology using overall clinical assessment as the reference standard has been utilized previously in studies of the utility of ^{111}In-labeled WBC scans for diagnosis of infection [2–4, 12].

Each reviewer made an independent assessment of the clinical utility of the scan. Scans were categorized as clinically useful if they definitely or possibly contributed to subsequent clinical management decisions made about the patient. They were categorized as not clinically useful if they did not contribute to the clinical management of the patient. In some cases it was impossible to determine whether the scan was helpful in patient management, and these scans were categorized as having an unclear contribution to diagnosis or management. Examples of categories of clinical utility (with illustrative quotations from the medical record) follow:

- Positive scan, helpful: "Pushed surgery to remove graft in setting of persistent bacteremia."
- Positive scan, possibly helpful: "Patient with prior methicillin-sensitive *Staphylococcus aureus* endocarditis with scan that lit up in the brain; computed tomography and magnetic resonance imaging scans done around the same time showed enhancing lesions concerning for abscesses."
- Positive scan, not helpful: "Scan consistent with arteriovenous graft infection but surgery wouldn't remove, so prolonged antibiotics."
- Negative scan, helpful: "Disseminated *Mycobacterium chelonae* infection, no sign of graft infection."
- Negative scan, not helpful: "Negative scan but clinically thought to have infected graft which was removed and found to be infected."

When independent observers disagreed on the scan result or clinical utility of the scan, the case was discussed to arrive at a consensus decision; a final consensus was reached in all cases.

Descriptive statistics were used to describe and compare characteristics of patients whose scans were clinically useful vs those whose were not. Correlation of interrater observations was assessed using the κ statistic. Sensitivity and specificity of ^{111}In-labeled WBC scans for diagnosis of infectious conditions were determined. Cases in which there were insufficient data to make a definitive diagnosis were excluded from the analysis of test sensitivity and specificity. Data analysis was performed using SAS version 9.3 (SAS Institute).

RESULTS

One hundred thirty-seven ^{111}In-labeled WBC scans were performed at our tertiary referral hospital during the 7-year study period. The number of scans that were performed each year decreased during the study period, from 26 scans in 2005 to 13 scans in 2011. Ninety-seven (71%) scans were performed on hospitalized patients, whereas the remaining scans were performed on outpatients. ^{111}In-labeled WBC scans were ordered by providers in a variety of specialties and subspecialties. Seventy-four (57%) scans were ordered by internal medicine specialists or subspecialists; 46 (36%) scans were ordered by general surgeons or surgical subspecialists, including 27 (21%) scans ordered by orthopedic surgeons; and 9 scans were ordered by miscellaneous other specialists (Table 2).

Scans were most commonly ordered to evaluate for osteomyelitis (n = 51 [37%]). Other scan indications included FUO (n = 37 [27%]), known other infection (n = 28 [20%]), possible vascular access infection (n = 16 [12%]), possible prosthetic device infection (n = 4 [3%]), and other (n = 1 [1%]). Ultimately, a definitive diagnosis of infection was made in 85 (62%) cases and a definitive diagnosis of a noninfectious condition was made in 32 (23%) cases. There were insufficient data to make a definitive diagnosis in 20 (15%) cases. Detailed description of scan indications, results, and final diagnoses is included in Table 3.

Table 2. Demographic and Clinical Features of Patients Who Underwent Indium 111–Labeled White Blood Cell Scans at Duke University Medical Center, 2005–2011

Feature	No. (%)
Total scans	137
Male	60 (44)
Race	
White	84 (61)
Black	47 (34)
Other	6 (4)
Age, y, mean (SD)	53 (17)
Age <18	6 (4)
Age >70	23 (17)
Setting	
Outpatient	40 (29)
Inpatient	97 (71)
Specialty	
Surgery	46 (36)
Orthopedics	27 (21)
General surgery	6 (5)
Other subspecialty	13 (10)
Medicine	74 (57)
General medicine	24 (19)
Infectious diseases	7 (5)
Other subspecialty	43 (33)
Pediatrics	6 (5)
Other	3 (2)
Missing	8

The overall sensitivity of WBC scans for diagnosing any infection was 0.43; the specificity for infection was 0.90. In addition, we also assessed the sensitivity and specificity for the 3 most common scan indications (Table 4). Overall, in our population the positive predictive value of a positive ^{111}In-labeled WBC scan for infection was 0.92, whereas the negative predictive value of ^{111}In-labeled WBC scans for infection was 0.37.

Interestingly, the independent reviewers disagreed regarding the scan result (positive vs negative) in 13 cases. These disagreements all related to ambiguity in the radiology reports, and were resolved after reevaluation using strict interpretations of the predefined study criteria. After initial, independent review, observers agreed on the clinical utility (helpful or not helpful) in 97 (70%) cases (κ = 0.45). The 2 observers discussed each case in which individual observations regarding clinical utility

Table 3. Description of Final Diagnoses by Indium 111–Labeled White Blood Cell Scan Indication, Result, and Utility: Duke University Medical Center, 2005–2011

Scan Indication	Result	Utility	Final Diagnosis	No. of Cases
Suspected osteomyelitis	Positive	Useful	Skin and soft tissue infection	2
			Chronic osteomyelitis	
			Tibia/fibula/femur	6
			Foot	2
			Sternum/clavicle	1
			Pelvis	1
			Chest pain	2
		Not useful	Chronic pain after surgery	1
			Infected spinal hardware	1
	Negative	Useful	Chronic pain	5
			Chronic pain after surgery	8
			Drug fever	1
			Endocarditis	1
			Septic arthritis	1
			Fracture nonunion	4
			Unknown	1
		Not useful	Skin and soft tissue infection	1
			Bacteremia	1
			Osteomyelitis	4
			Prosthetic joint infection	1
			Chronic pain after surgery	1
			Chronic mastoiditis	3
			Unknown	2
	Indeterminate		Wound infection/bacteremia	1
Fever of unknown origin	Positive	Useful	Graft-vs-host disease	1
			Pneumonia	1
		Not useful	Bacteremia	2
			Disseminated infection	1
			Intra-abdominal infection	1
			Unknown	1
	Negative	Useful	Chronic pain	1
			Post-op fever	2
			Graft-vs-host disease	1
			Bacteremia	3
			Rheumatologic	2
			Unknown	1
		Not useful	Pneumonia	2
			Endocarditis	2
			Postoperative fever	2
			Graft-vs-host disease	2
			Rheumatologic	1
			Thrombophlebitis	1
			Drug fever	1
			Factitious disorder	1
			Splenic abscess	1
			Unknown	5
	Indeterminate		Unknown	2

Table 3 continued.

Scan Indication	Result	Utility	Final Diagnosis	No. of Cases
Suspected graft infection	Positive	Useful	Vascular graft infection	6
		Not useful	Bacteremia, possible endocarditis	1
	Negative	Useful	Graft leak/pseudoaneurysm	1
			Endocarditis	1
			Disseminated mycobacterial infection	1
			Unknown	1
		Not useful	Bacteremia	2
			Vascular graft infection	1
			Vertebral osteomyelitis	1
	Indeterminate		Bacteremia	1
Known other infection	Positive	Useful	Prosthetic joint infection	1
			Brain abscess	1
		Not useful	Bacteremia	5
			Osteomyelitis	2
			Disseminated candidiasis	1
			Skin and soft tissue infection	1
	Negative	Useful	Vascular graft infection	1
			Vascular device infection	1
		Not useful	Bacteremia	7
			Endocarditis	2
			Tunneled catheter infection	2
			Osteomyelitis	2
			Vascular device infection	1
			Mycotic aneurysm	1
Possible prosthetic device infection	Negative	Useful	Aseptic prosthetic joint loosening	1
		Not useful	Vascular device infection	2
	Indeterminate		Painful prosthesis	1
Other	Negative	Useful	Wound infection	1

differed to determine a consensus decision. After discussion, the clinical utility could not be determined in 5 cases.

Of the 132 evaluable cases, 56 (42%) scans definitely contributed to clinical management and 7 (5%) scans possibly contributed to clinical management, although other diagnostic tests provided similar information. Thus, 63 (48%) scans were deemed clinically useful in the management of patients (Table 5). The clinical utility varied by scan result and indication for the scan. Positive scans were more often found to be clinically useful than negative scans (24/41 [59%] for positive scans vs 39/91 [43%] for negative scans). Scans were more helpful for indications of osteomyelitis (35/50, 70% useful) or vascular graft infection (10/15, 67% useful), and less helpful for evaluation of FUO (12/35, 34% useful).

Table 4. Sensitivity and Specificity of Indium 111–Labeled White Blood Cell Scans: Overall and Indication-Specific Results

Scan Indication[a]	Sensitivity	Specificity
All suspected infections	36/83 (0.43)	28/31 (0.90)
Fever of unknown origin	5/15 (0.33)	9/10 (0.90)
Osteomyelitis	13/25 (0.52)	16/18 (0.89)
Vascular graft infection	7/13 (0.53)	1/1 (1.00)

[a] Cases for which either test result or final diagnosis were unable to be determined were excluded from this analysis.

CONCLUSIONS

We report our academic medical center's 7-year experience of the utilization and utility of ^{111}In-labeled WBC scans for diagnosing suspected infections. Overall, ^{111}In-labeled WBC scan results impacted clinical care less than half of the time at our center. We believe that our findings are meaningful and must be considered by clinicians in the process of diagnostic decision making.

Our approach to this evaluation is unique, as we focused primarily on the clinical utility rather than traditional measures of diagnostic accuracy. We assert that diagnostic tests provide benefit (both to clinicians and consumers of medical care) when the results meaningfully impact subsequent clinical care. In this way, both positive and negative tests can be highly beneficial. Others have reported clinical utility of nuclear imaging tests as the proportion of tests that led to a final diagnosis. Thus,

Table 5. **Clinical Utility of Indium 111–Labeled White Blood Cell Scans by Clinical Indication, Scan Result, and Final Diagnosis**

Factor	Total	Overall Utility[a], No. (%)	Definite Contribution[a], No. (%)	Possible Contribution[a], No. (%)
All cases	132	63 (48)	56 (42)	7 (5)
Reason for scan				
Osteomyelitis	50	35 (70)	30 (60)	5 (10)
FUO	35	12 (34)	11 (31)	1 (3)
Other known infection	28	4 (14)	3 (11)	1 (4)
Vascular graft infection	15	10 (67)	10 (67)	. . .
Prosthetic device infection	3	1 (33)	1 (33)	. . .
Other	1	1 (100)	1 (100)	. . .
Scan result				
Positive	41	24 (59)	17 (41)	7 (17)
Negative	91	39 (43)	39 (43)	. . .
Final diagnosis				
Infection	83	30 (36)	24 (29)	6 (7)
Noninfectious	31	26 (84)	25 (81)	1 (3)
Indeterminate	18	7 (39)	7	. . .

Abbreviations: FUO, fever of unknown origin.

[a] Utility determined by review of medical record by 2 independent reviewers as follows: overall utility—scans definitely or possibly contributed to the clinical management of the patient; definite contribution—scans were felt to definitely impact subsequent clinical management; possible contribution—scans may have impacted clinical management but other tests provided the same or similar information.

only positive tests are potentially useful by this definition of clinical utility [13, 14]. Furthermore, we distinguish clinical utility from clinical accuracy. An accurate test that does not impact clinical decision making is of little value. We suspect that similar assessments of the added value of diagnostic tests will become common as the medical community faces increasing pressures to control costs.

The utility of ^{111}In-labeled WBC scans differed depending on the clinical indication for the scan. Scans were more helpful in the management of suspected vascular access infections and osteomyelitis than FUO. This is not unexpected, given the heterogeneity of diseases encompassed by the syndrome of FUO and the known difficulty in diagnosing the etiology of FUO even in the modern era of improved cross-sectional imaging [15]. Positive scans were more likely to be helpful than negative scans. The sensitivity of ^{111}In-labeled WBC scans for the diagnosis of infectious conditions was <50%, which is lower than values reported by others [2, 3, 7, 8, 10]. Therefore, the decreased utility among negative scans at our center may reflect an appropriate perception by prescribing physicians of the uncertainty of negative test results.

Clear written and spoken communication between prescribing physicians and consultants is essential to medical practice. This is exemplified by our findings. Independent reviewers initially disagreed regarding the scan result in approximately 10% of cases. The disagreement was felt to relate to ambiguous wording of radiology reports. As noted above, ^{111}In-labeled WBC scans are performed infrequently at our hospital. Inexperience by providers and interpreting radiologists may have contributed to uncertainty that led to difficulty in conveying or interpreting results. Furthermore, poor interrater agreement has been previously reported for leukocyte scintigraphy. In one study, only 65% of radiologists provided the same interpretation (high, intermediate, or low probability of infection), and an interpretation of "intermediate probability" was given nearly 20% of the time [16]. Clinical utility of any test will be influenced by the consistency and clarity with which findings are reported. A standardized way of reporting scan results (as opposed to free-text reporting) may be one way to improve the clinical utility of complex tests such as ^{111}In-labeled WBC scans; such standardized reporting using checklists has been advocated for other radiographic studies [17].

While ^{111}In-labeled WBC scintigraphy was the most common method of nuclear imaging utilized for the detection of infection at our institution during the time of the study, other radiopharmaceuticals can be used for this purpose. Gallium 67 (^{67}Ga) citrate accumulates in body sites due to increased vascular permeability; therefore, one advantage of gallium scans is that no ex vivo cell labeling is required. However, in practice, the utility of gallium scans is limited by their lack of specificity and requirement for waiting periods up to 72 hours between injection and imaging [1, 18]. ^{111}In oxine and Technetium 99m (^{99m}Tc)-hexamethylpropyleneamine oxime (HMPAO) are the most common agents used to label WBCs [19]. The 2 labeling techniques have some important differences. ^{111}In-labeling is recommended over ^{99m}Tc for imaging the urinary tract and gallbladder, because excretion of ^{99m}Tc occurs via these routes [18–20]. ^{111}In labeling is preferred for indications of chronic osteomyelitis and FUO, whereas ^{99m}Tc labeling may play a specific role in evaluation of inflammatory bowel disease or acute soft tissue infections [19, 20]. Other radiopharmaceuticals, including cytokines and antimicrobials, have been proposed but are not available for clinical use in the United States at this time [18]. Unfortunately, no one modality performs superiorly for all clinical scenarios, and, thus, understanding the strengths and weaknesses of each can help providers pursue the test most likely to provide the greatest value.

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET), which is primarily used for localization of malignancy, has also demonstrated utility for the detection of infection or inflammation [18, 21]. In one retrospective study, FDG-PET imaging was abnormal in 15 of 35 (43%) patients with FUO, and led to the diagnosis of the etiology in 13 (37%) patients. In the same study, FDG-PET was abnormal in 38 of 55 (69%) cases of suspected localized infection or inflammation and contributed to the eventual diagnosis in 36 (65%) cases [13]. The authors reported high sensitivity (93%, 100%) and specificity (90%, 89%) of FDG-PET for the diagnosis of FUO and localized infection, respectively [13]. Pill et al prospectively compared FDG-PET to traditional methods of ^{99m}Tc bone and ^{111}In-labeled WBC scintigraphy to differentiate aseptic loosening from periprosthetic infection in patients with painful hip prostheses [22]. FDG-PET demonstrated a sensitivity and specificity of 95% and 93%, respectively, for infection whereas the ^{99m}Tc bone scan and ^{111}In-labeled WBC together had a sensitivity and specificity of 50% and 95%, respectively. Similarly, Seshadri et al prospectively compared FDG-PET to ^{111}In-labeled WBC scintigraphy for the evaluation of FUO [23]. The sensitivity of FDG-PET for determining the etiology of FUO was 86% whereas the sensitivity of ^{111}In-labeled WBC scintigraphy was only 20% [23]. Thus, FDG-PET imaging has demonstrated greater sensitivity than ^{111}In-labeled WBC scintigraphy in small, prospective comparisons. At this time, high cost and lack of reimbursement by insurance companies for noncancer indications hinder FDG-PET's more widespread use. However, FDG-PET may eventually supplant other modalities of nuclear imaging for the diagnosis of suspected infection.

We acknowledge several limitations to the current study. First, the study was performed at a single tertiary medical center in which the utilization of ^{111}In-labeled WBC scans was relatively infrequent. Our results may not be generalizable to other settings, especially those in which nuclear imaging studies are performed commonly or are incorporated into established diagnostic algorithms. Second, assessing the clinical utility as we have done is inherently subjective. Despite using standardized, a priori definitions of clinical utility, independent reviewers initially disagreed in a minority of cases. Furthermore, determination of utility was made by retrospective review, requiring reviewers to extrapolate cause–effect relationships from the electronic medical record. If clinicians had been interviewed in real time to assess the role of the scans in decision making, the perceived utility of the scans would possibly have been higher. However, prospective interviews may have introduced bias by impacting scan prescribing practices or subsequent patient care decisions.

In the current era of increasing emphasis on cost-conscious and accountable care, appropriate utilization of expensive and logistically challenging tests is vital. ^{111}In-labeled WBC scans are clinically useful in a minority of cases. Targeting ordering of these scans for conditions in which they are most likely to impact clinical care, including vascular graft infections and osteomyelitis, would optimize resource utilization.

Notes

Financial support. This work was supported by the Division of Infectious Diseases at Duke University Medical Center.

Potential conflicts of interest. All authors: No potential conflicts.

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