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Radiolabeled WBC Scintigraphy in the Diagnostic Workup of Patients With Suspected Device-Related Infections

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OBJECTIVES The aim of this study was to investigate the diagnostic performance of ^{99m}Tc-hexamethypropylene amine oxime labeled autologous white blood cell (^{99m}Tc-HMPAO-WBC) scintigraphy in patients with suspected infections associated with cardiovascular implantable electronic devices (CIEDs).

BACKGROUND Early, definite recognition of CIED-related infections combined with accurate localization and quantification of disease burden is a prerequisite for optimal treatment strategies.

METHODS All 63 consecutive patients underwent clinical examination, blood chemistry, microbiology, and echography of the cardiac region/venous pathway of the device. Final diagnosis of infection was established in 32 of 63 patients and in 23 of 32 by microbiology.

RESULTS Sensitivity of ^{99m}Tc-HMPAO-WBC single-photon emission computed tomography/computed tomography (SPECT/CT) was 94% for both detection and localization of CIED-associated infection. SPECT/CT imaging had a definite added diagnostic value over both planar and stand-alone SPECT. Pocket infection was often associated with lead(s) involvement; the intracardiac portion of the lead(s) more frequently exhibited ^{99m}Tc-HMPAO-WBC accumulation and presented the highest rate of complications, infectious endocarditis, and septic embolism. Two false negative cases and no false positive results were observed. None of the patients with negative ^{99m}Tc-HMPAO-WBC scintigraphy developed CIED-related infection during follow-up of 12 months. Echography of the cardiac region/venous pathway of the device had 90% specificity, but low sensitivity (81% when intracardiac lead[s] infection only was considered). The Duke criteria had 31% sensitivity for the *definite* category (100% specificity) and 81% for the *definite* and *possible* categories (77% specificity).

CONCLUSIONS ^{99m}Tc-HMPAO-WBC scintigraphy enabled the confirmation of the presence of CIED-associated infection, definition of the extent of device involvement, and detection of associated complications. Moreover, ^{99m}Tc-HMPAO-WBC scintigraphy reliably excluded device-associated infection during a febrile episode and sepsis, with 95% negative predictive value. (J Am Coll Cardiol Img 2013;■:■–■)

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Use of cardiovascular implantable electronic devices (CIEDs) has increased significantly over the past decade due to growing evidence of improved quality of life and survival among certain groups of patients (1); such devices include the permanent pacemaker, the implantable cardioverter-defibrillator, and cardiac resynchronization therapy. Associated complications, particularly infections, have risen disproportionally higher than the growth of newly implanted devices (2). The rate of CIED-related infections varies widely between 1% and 7% (3), with significant morbidity and mortality, especially in cases of delayed diagnosis (4). Therefore, strategies to facilitate early diagnosis are crucial for a favorable clinical outcome.

Diagnostic workup of CIED-related infections is problematic because patients can present with a variety of manifestations, including subtle signs of systemic or local infection (5). The decision of whether to medically treat the infection and/or to remove the device represents a further crucial point, because it implies evaluation of response to antimicrobial therapy and selection of the optimal time to re-implant (6).

ABBREVIATIONS AND ACRONYMS

[^{18}F]FDG PET/CT = ^{18}F-labeled fluorodeoxyglucose positron emission tomography/computed tomography

^{99m}Tc-HMPAO-WBC = Technitium-99m–hexamethyl propylene amine oxime–labeled autologous white blood cell

CIED = cardiovascular implantable electronic device

CT = computed tomography

SPECT = single-photon emission computed tomography

Final diagnosis of CIED-associated infection is generally based on microbiological tests (blood cultures and culture of material from exposed sites of implantation) and ultrasound evaluation of the cardiac region (either transthoracic and transesophageal) and of the venous pathway of the device. These tests constitute the basis for defining a patient's risk for CIED-related infection according to the Duke criteria (7). However, in cases of CIED-related infection, the Duke criteria, originally developed for the diagnosis of infectious endocarditis, may be inadequate; even with the addition of clinical parameters (8), the possibility of missing the presence of, and/or underestimating the extent of, infection remains high (5).

There is growing evidence that positron emission tomography used with computed tomography with ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG PET/CT) improves the diagnosis of CIED-related infection (9–11). On the other hand, in the era of high spatial resolution hybrid systems for single-photon emission computed togmography (SPECT) used with CT (SPECT/CT), scintigraphy with radiolabeled autologous white blood cells (WBCs) represents a valuable option for imaging patients with suspected CIED-related infection, as already demonstrated in a number of other clinical conditions, such as native and prosthetic valve–related endocarditis (12). These functional imaging modalities are based on the ability to detect and localize metabolically active cells, such as those involved in inflammation and infection. By following the pattern of radiolabeled WBC accumulation over time and by using well-defined criteria for interpretation (13), it is possible to discriminate active infection from inflammatory changes (e.g., post-surgical changes, foreign-body reactions) and to define the extent of active infection.

This study investigated the diagnostic performance of ^{99m}Tc-hexamethypropylene amine oxime–labeled autologous WBCs (^{99m}Tc-HMPAO-WBC) SPECT/CT in consecutive patients referred to the Division of Cardiology or Infectious Diseases, University Hospital of Pisa, Pisa, Italy, for suspected CIED-related infection.

METHODS

Study design and patient population. Between June 2007 and June 2011, a total of 63 consecutive patients (47 men and 16 women; mean age 68.6 ± 13.9 years; median age 70 years [range 27 to 87 years]) were referred for scintigraphy with radiolabeled autologous WBCs (^{99m}Tc-HMPAO-WBC), recording both planar and SPECT/CT acquisitions, and results were retrospectively evaluated. All patients provided informed consent to undergo the procedure. Workup consisted of clinical examination, blood chemistry including WBC count, C-reactive protein, erythrocyte sedimentation rate, acute phase proteins, electrophoresis, urinalysis, transthoracic and transesophageal echocardiography, and ultrasound evaluation of the venous pathway. Three sets of peripheral venous blood samples were obtained for cultures, including at least 1 aerobic and 1 anaerobic sample (14). Scintigraphy was performed in all cases of unconfirmed diagnosis of CIED-related infection at the end of the described conventional procedures. After ^{99m}Tc-HMPAO-WBC, treatment was decided on the basis of the degree of certainty of diagnosis of CIED-related infection as results of conventional tests and clinical guidelines, as follows: 35 patients were treated with device extraction followed by antimicrobial therapy, as previously described (15); 9 patients, with antimicrobial therapy alone; and 11 patients, with other disease-specific surgical procedures. Eight patients received no treatment. In patients with a high clinical suspicion of CIED-related infection based on either a positive blood culture (n = 12) or diagnostic echocardiography (n = 7), the results of ^{99m}Tc-

HMPAO-WBC were not used to guide final decisions on management because these patients underwent device extraction followed by antimicrobial therapy (Fig. 1). In cases of antimicrobial therapy alone or no treatment, clinical follow-up of at least 12 months was available for final classification. All 9 patients who underwent antimicrobial therapy alone had repeat ^{99m}Tc-HMPAO-WBC scintigraphy at the end of treatment. A total of 75 examinations were therefore performed (63 baseline and 12 follow-up studies); in particular, 9 patients had repeat studies (6 with one follow-up scan after 6 months, 3 with two follow-up scans at 6 to 9 and 12 months).

The main clinical features of patients and types of devices implanted are reported in Table 1. Final diagnosis of CIED-associated infection was established in 32 of 63 patients (Table 2); in 23 of 32 patients, diagnosis was confirmed by microbiology after extraction of the device. In the remaining 9 of 32 cases, diagnosis was obtained with clinical follow-up of at least 12 months based on negative findings on clinical examination, sequential blood tests, transthoracic and transesophageal echocardiography, ultrasound evaluation of the venous pathway, and ^{99m}Tc-HMPAO-WBC scintigraphy following antimicrobial treatment.

Staphylococcus spp. was the microorganism most frequently involved in CIED-associated infection (12 of 32), followed by *Streptococcus* spp. (8 of 32); *Enterococcus* spp. (3 of 32); Enterobacteriaceae, *Micrococcus,* and *Candida* spp. (2 patients each); and *Pseudomonas aeruginosa, Acinetobacter baumanni,* and *Propionibacter acnes* (1 patient each).

Infection occurred most frequently early after implantation (6 of 8 patients evaluated at <1 month and 5 of 13 cases evaluated at 1 to 3 months after implantation). Semi-late and late infections were observed in 8 of 18 and in 13 of 22 patients, respectively (Table 1). Nineteen of 32 infections occurred after the second implantation procedure.

Radiolabeling and acquisition protocol. Autologous radiolabeled WBCs were prepared according to the European Association of Nuclear Medicine guidelines for labeling WBCs with ^{99m}Tc-HMPAO (16,17). Radiolabeling efficiency was always between 70% and 85%; viability of the radiolabeled WBCs was always evaluated by the Tripan blue exclusion test before reinfusion. Radiolabeling of WBCs with ^{99m}Tc was preferred over the radiolabeling with ^{111}In for both radiation safety (0.017 mSv/MBq with a recommended administered activity of 185–370 MBq for ^{99m}Tc vs. 0.59 mSv/MBq with a recommended administered activity of 10–18.5 MBq for ^{111}In) (13,18) and imaging quality when performing SPECT/CT.

Whole-body and spot planar images were obtained after 30 min, then 4 to 6 h (early images) and 20 to 24 h (delayed images) after reinfusion of 370 to 555 MBq of ^{99m}Tc-HMPAO-WBC. SPECT/CT of the chest was performed in all patients at 6 h and repeated at 24 h in cases of negative or doubtful imaging at 6 h. Images were acquired using a dual-head, variable-angle SPECT/CT gamma camera (Hawkeye and Discovery 670, GE Healthcare, Little Chalfont, United Kingdom) as previously reported (12). Both CT attenuation–corrected and –noncorrected SPECT images were

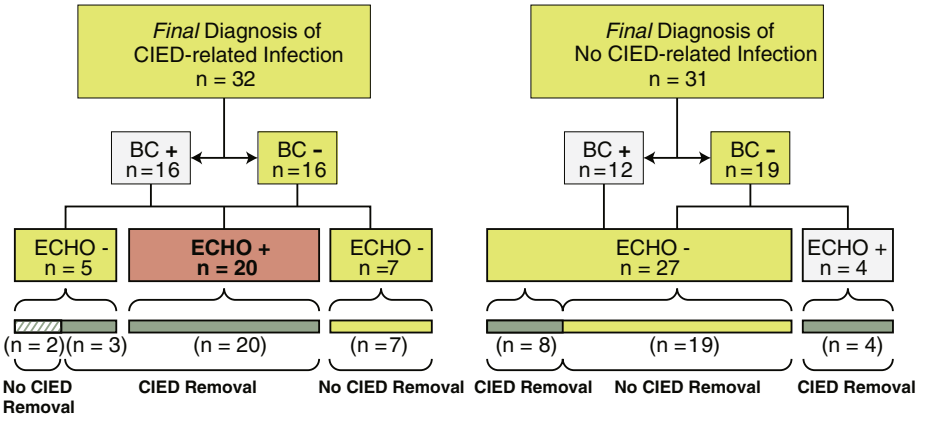


Figure 1. Clinical Management

Clinical management of patients included in the study according to the final diagnosis of cardiovascular implantable electronic device (CIED)-related infection **(left panel)** or exclusion of CIED-related infection **(right panel)**. BC = blood culture; ECHO = echocardiography.

Table 1. Types of Cardiac Devices and Main Clinical Features of the Patients Included in the Study (N = 63)

Device type	
1-Chamber PM	30 (48)
Infection	12/30 (40)
2-Chamber PM	17 (27)
Infection	7/17 (41)
Temporary PM	2 (3)
Infection	1/2 (50)
1-Chamber ICD	9 (14)
Infection	7/9 (78)
2-Chamber ICD	5 (8)
Infection	3/5 (60)
Risk factors	
Diabetes	17 (27)
Renal failure	11 (17)
Long-term corticoid	7 (11)
Previous infection	8 (13)
Recent invasive procedure	30 (48)
Fever	35 (55)
Time from device implantation, months	
≤1	10 (16)
Infection	6/10 (60)
>1–3	13 (21)
Infection	5/13 (38)
>3–12	18 (28)
Infection	8/18 (44)
>12	22 (35)
Infection	13/22 (59)
Local inflammation signs/symptoms	
Pain	16 (25)
Tenderness	14 (22)
Erythema	8 (13)
Purulent drainage	3 (5)
Blood test	
ESR	49 (77)
PCR	42 (67)
Leukocytosis	29 (46)
Microbiological blood culture results	
Positive	28 (44)
Negative	37 (56)*

Values are n (%). *During antibiotic therapy in 29 of 63 patients; 5 patients presented with either positive EC or pocket culture.
CRP = C-reactive protein; EC = electrocatether; ESR = erythrocyte sedimentation rate; ICD = implantable cardioverter defibrillator; PCR = polymerase chain reaction; PM = pacemaker.

Table 2. Results of Microbiological Evaluation/Culture Results Before and After Device Removal in Patients With CIED-Associated Infection (n = 32)

Blood culture	
Positive	16 (50)
Negative	16 (50)*
Microbiology after device removal†	23 (74)

Values are n (%). *During antibiotic therapy in 8 of 16 patients. †Extraction was performed in a total of 35 patients, including 11 in whom CIED-associated infection resolved; 9 of 32 patients with CIED infection did not undergo extraction.
CIED = cardiovascular implantable electronic devices.

evaluated in the coronal, transaxial, and sagittal planes, as well as in tridimensional maximal-intensity projection cine mode. Matching pairs of x-ray transmission and radionuclide emission images were fused using Xeleris software (GE Healthcare), and hybrid images of overlying transmission and emission data were generated.

Interpretation criteria. All images were re-evaluated, independently, by 2 experienced nuclear physicians aware of the patients' clinical history and of the results of prior conventional imaging. Images were first visually inspected to exclude misregistration between the SPECT and the CT components. Thereafter, for all sets of images, the presence and location of any focus of abnormal radioactivity accumulation indicating infection was evaluated. The scintigraphic studies were classified as *negative* when no sites of abnormal uptake were observed in the SPECT/CT images, or as *positive* for infection when at least 1 focus of abnormal uptake characterized by a time-dependent increase in radioactivity between early and delayed images was observed (13). When present, focal uptake indicating infection was further classified as: 1) isolated pocket infection; 2) isolated lead infection at either the intravascular or the intracardiac portion of the lead; 3) pocket and lead infection (either intravascular or intracardiac portion); 4) concomitant endocarditis; 5) extracardiac site(s) of infection consistent with embolism; or 6) other infection.

Data analysis. Results of ^{99m}Tc-HMPAO-WBC scintigraphy were correlated with those of ultrasonography (echocardiography + soft tissue/venous ultrasound), with the Duke criteria classification, and with final microbiological or clinical diagnosis. Furthermore, the ability to identify concomitant endocarditis as well as septic emboli was considered in the assessment of the ability of ^{99m}Tc -HMPAO-WBC scintigraphy to define disease burden.

For site-based analysis, results of planar, stand-alone SPECT, and SPECT/CT imaging were compared. Stand-alone SPECT and SPECT/CT were considered to have a definite added value if they provided data that could not be obtained from planar imaging concerning the presence of infection or its precise location. The contribution of SPECT/CT

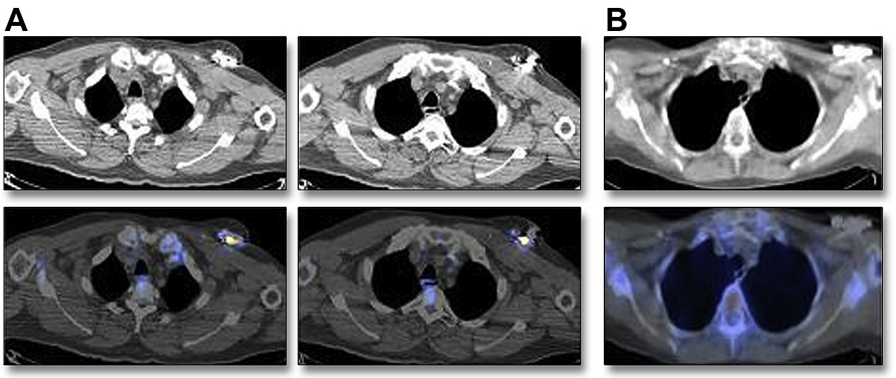


Figure 2. ^{99m}Tc-HMPAO-WBC of CIED-Related Infection Involving the Pocket

(A) Tecnitium-99m–hexamethyl propylene amine oxime–labeled autologous white blood cell (^{99m}Tc-HMPAO-WBC) scintigraphy in a patient with localized pocket infection, with transaxial slices shown at different levels (computed tomography [CT] sections in **upper panels,** corresponding fused single-photon emission computed tomography [SPECT]/CT sections in **lower panels**). Obvious focal accumulation of radiolabeled WBCs at the pocket. **(B)** A normal scintigraphic pattern, shown for comparison.

was considered with special attention to the possibility of anatomically localizing the exact site of infection.

Statistical analysis. All values are expressed as median and range, as is standard for nonparametric data. The Pearson chi-square test was employed for comparing nominal data between groups. Interobserver agreement was determined and expressed in a weighted kappa, which corrects for agreement by chance. The higher the kappa, the higher the agreement, with a maximum value of 1.0 (<0.0 = no agreement; 0.0 to 0.19 = poor agreement; 0.20 to 0.39 = fair agreement; 0.40 to 0.59 = moderate agreement; 0.60 to 0.79 = substantial agreement; and 0.80 to 1.00 = almost perfect agreement) (19). In cases of disagreement between the 2 observers, a final consensus reading was performed. Sensitivity, specificity, accuracy, and positive and negative predictive values of echocardiography, Duke criteria, and ^{99m}Tc-HMPAO-WBC planar, stand-alone SPECT, and SPECT/CT imaging were calculated based on the final diagnosis, with 95% confidence intervals (CIs), and compared using the McNemar test.

RESULTS

^{99m}Tc-HMPAO-WBC scintigraphy in patients with CIED-related infections. By adopting the interpretation

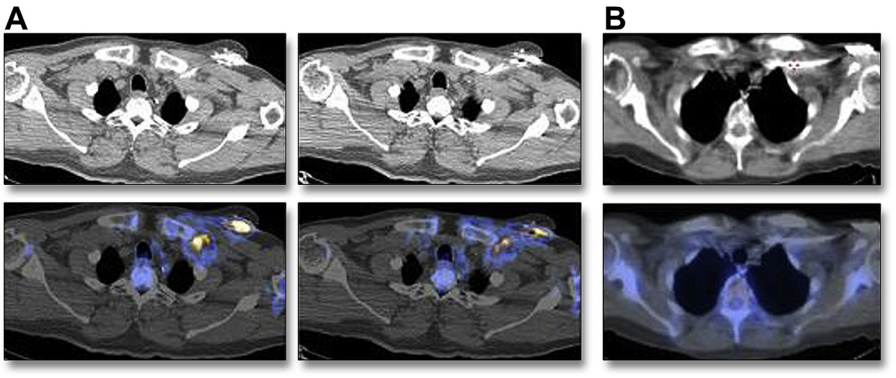


Figure 3. ^{99m}Tc-HMPAO-WBC of Ascertained CIED-Related Infection Involving the Pocket and the Intravascular Portion of the Lead

(A) ^{99m}Tc-HMPAO-WBC scintigraphy in a patient with clinically ascertained pocket infection, with transaxial slices shown at different levels (CT sections in **upper panels,** corresponding fused SPECT/CT sections in **lower panels**). Obvious focal accumulation of radiolabeled WBCs involving both the pocket and the intravascular portion of the lead. **(B)** A normal scintigraphic pattern is shown for comparison. Abbreviations as in Figure 2.

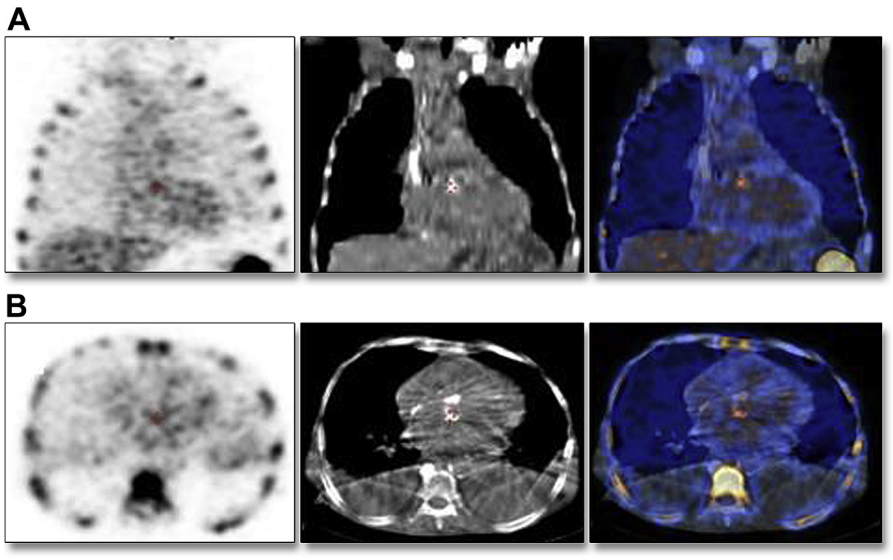


Figure 4. ^{99m}Tc-HMPAO-WBC of Suspected CIED-Related Infection at the Intracardiac Lead

^{99m}Tc-HMPAO-WBC scintigraphy in a patient with suspected CIED infection. Obvious focal accumulation of radiolabeled WBCs at the heart region in the SPECT coronal **(A, left panel)** and transaxial images **(B, left panel);** fused SPECT/CT sections exactly localized the focus of infection at the intracardiac lead **(right panels)**. CT images are shown in the **middle panels**. Abbreviations as in Figure 2.

criteria described earlier for scintigraphic detection of infection evaluating the best-performing imaging, that is, SPECT/CT, it was possible to classify all of the scans as either frankly positive or frankly negative and therefore without equivocal result. The kappa value for interobserver agreement was 0.951 (95% CI: 0.909 to 1.000).

The ^{99m}Tc-HMPAO-WBC scans were totally negative in 22 of 63 cases. At least 1 area with focal accumulation of the radiolabeled WBCs was detected in the remaining 41 patients.

^{99m}Tc-HMPAO-WBC scintigraphy was true positive in 30 of 32 patients with final diagnosis of CIED-associated infection (94%). The two false negative scans were observed in patients with CIED-related infections caused by *Candida* and *Enterococcus* spp. (final diagnosis obtained by culture of the leads). One of these 2 patients also had false negative echocardiography and was classified as *rejected* infection according to the Duke criteria; the case of second false negative scintigraphy was true positive on echocardiography and was classified as *definite* infection according to the Duke criteria. Both of the latter patients were on antimicrobial therapy at the time of scintigraphy. There were no false positive scans for CIED-related infection. Figure 2 shows an example of positive ^{99m}Tc-HMPAO-WBC scintigraphy for infection localized at the pocket. Figures 3 and 4 show the scintigraphic pattern of infection localized at the intravascular and intracardiac portions of the leads, respectively.

SPECT/CT acquisition provided higher accuracy both for detecting infection and for localizing ^{99m}Tc-HMPAO-WBC accumulation at any portion of the device, at the heart valves, or at other noncardiac sites of infection in the thoracic and mediastinal space. SPECT/CT acquisitions changed the final classification of the scan from negative to positive for CIED-associated infection in 15 of 32 of the cases compared with the standard planar and 9 of 32 compared with SPECT-alone acquisition (chi-square: 4.5; $p = 0.03$) (Table 3). No false positive findings due to artefact were detected in either the attenuation-corrected or non–attenuation-corrected images.

Table 4 summarizes the results of ^{99m}Tc-HMPAO-WBC scintigraphy (considering the best nuclear imaging technique, i.e., SPECT/CT), of echocardiography, and of classification according to the Duke criteria in the cases of a final diagnosis of CIED-related infection. Table 5 correlates the results of ^{99m}Tc-HMPAO-WBC scintigraphy with the results of echocardiography and with the Duke classification, stratifying the patients according to the site of radiolabeled WBC accumulation, as follows: at the pocket, at the intravascular and/or intracardiac

Table 3. Results and Diagnostic Performance of ^{99m}Tc-HMPAO-WBC Planar, SPECT, and SPECT/CT Acquisitions in Patients With CIED-Associated Infection (n = 32)

	Planar	SPECT	SPECT/CT
Result, n/N			
Positive for CIED	15/32	21/32	30/32
Doubtful for CIED infection	11/32	9/32	–
Negative for CIED infection	6/32	2/32	2/32
Correct extent for device infection	12/32	21/32	30/32
Correct exclusion device involvement	36/43*	42/43	43/43
Correct detection of embolism	12/18†	13/18†	15/18†
Correct detection of IE	3/6	4/6	6/6
Positive for other infections	9/15	13/15	15/15
Correct extent for other sites of infection	7/15	11/15	15/15
Diagnostic performance, 95% CI‡			
Sensitivity	53.1 (40.2–65.6)	71.9 (58.9–82.1)	93.7 (83.9–98)
Specificity	83.9 (72–91.5)	96.8 (87.9–99.4)	100 (92.8–100)
Accuracy	68.3 (55.2–79.1)	84.1 (72.3–91.7)	96.8 (88–99.4)
Positive predictive value	77.3 (64.7–86.5)	95.8 (86.6–99)	100 (92.8–100)
Negative predictive value	63.4 (50.3–74.9)	76.9 (64.3–86.2)	93.9 (84.1–98.1)

*Including 5 false positive cases due to sternal osteomyelitis and mediastinitis. †Including 3 false negative cases due to ophthalmitis and cerebral infection. ‡Planar versus SPECT: chi-square: 0.4, p = 0.5; planar versus SPECT/CT: chi-square: 3.5, p = 0.06; and SPECT versus SPECT/CT: chi-square = 4.5, p = 0.03 (McNemar test).
^{99m}Tc-HMPAO-WBC = Tecnitium-99m–hexamethyl propylene amine oxime–labeled autologous white blood cell; CI = confidence interval; CT = computed tomography; IE = infectious endocarditis; SPECT = single-photon emission CT.

portion of the lead(s), and at both the pocket and the lead(s). Sites of ^{99m}Tc-HMPAO-WBCs accumulation consistent with additional infections (n = 38) are also indicated. Particular attention was paid to the identification of concomitant infectious endocarditis (6 cases) (Fig. 5) and distant septic embolism (osteomyelitis, n = 6; vascular graft infection and lung infection, n = 4 each; and septic embolism in the spleen, n = 1). Septic embolism causing ophthalmitis or cerebral infection (1 case each), detected on CT, remained undiagnosed on radiolabeled WBC scanning.

Blood cultures. Blood cultures were positive in only 28 of 63 of the patients (16 of 32 of the cases of confirmed CIED-related infection); 28 of 35 of the blood culture–negative patients with CIED-associated infection were on antimicrobial treatment at the time of assessment. All 5 cases of CIED-associated infection with positive blood culture and negative transesophageal echocardiography and intact pocket had true positive ^{99m}Tc-HMPAO-WBC SPECT/CT examinations.

^{99m}Tc-HMPAO-WBC SPECT/CT ruled out device involvement during a febrile episode and sepsis (20 of 63 with positive blood culture), correctly excluding the presence of device involvement in 31 of 63 cases.

^{99m}Tc-HMPAO-WBC scintigraphy in patients without CIED-related infection. As to the 11 baseline scans showing focal accumulation of radiolabeled WBCs in patients without CIED-related infection, scintigraphy actually detected alternative sites of infection, with sensitivity and specificity of 93% and 91%, respectively) (Table 6). These patients were subsequently treated according to standard procedures as indicated for each clinical condition, and none, including patients with positive blood cultures, developed CIED-related infection during follow-up.

Follow-up studies. On follow-up studies performed 6 to 9 months after baseline scintigraphy, all of the sites of radiolabeled WBC accumulation were resolved in 7 of 9 patients, thus allowing for the discontinuation of antimicrobial treatment. In the remaining 2 patients, ^{99m}Tc-HMPAO-WBC positivity resulted in prolonged medical treatment, which was stopped only after normal findings on a third ^{99m}Tc-HMPAO-WBC scintigraphy performed 6

Table 4. Results of ^{99m}Tc-HMPAO-WBC Scintigraphy, Echocardiography, and Duke Criteria According to the Final Diagnosis of CIED Infection With All Examinations Performed at Baseline*

	^{99m}Tc-HMPAO-WBC	Echocardiography	Duke Criteria		
			Definite	Possible	Rejected
CIED infection (n = 32)			10/32	16/32	6/32
Positive	30/32	20/32			
Negative	2/32	12/32			
No CIED infection (n = 31)			0/31	8/31	23/31
Positive	0/31	4/31			
Negative	31/31	27/31			
Diagnostic performance, 95% CI					
Sensitivity	93.7 (83.9–98)	62.5 (49.4–74.1)	31.3† (20.5–44.3)	81.3 (69–89.6)	–
Specificity	100 (92.8–100)	87.1 (75.7–93.8)	100† (92.8–100)	74.2‡ (61.4–84)	–
Accuracy	96.8 (88–99.4)	74.6 (61.8–84.4)	65.1 (51.9–76.4)	52.4‡ (65.2–86.9)	–
Positive predictive value	100 (92.8–100)	83.3 (71.4–91.1)	100† (92.8–100)	76.5‡ (63.8–85.9)	–
Negative predictive value	93.9 (84.1–98.1)	69.2 (56.2–79.9	58.5† (45.4–70.5)	79.3‡ (66.9–88.1)	–

*^{99m}Tc-HMPAO-WBC versus echocardiography: chi-square: 2.6, p = 0.1; ^{99m}Tc-HMPAO-WBC versus Duke Criteria considering as positive for IE only the "definite" category: chi-square: 20, p < 0.001;^{99m}Tc-HMPAO-WBC versus Duke Criteria considering as positive for IE both the *definite* and *possible* categories: chi-square: = 1.3, p = 0.25 (McNemar test). †Considering as positive for IE the only *definite* category. ‡Considering as positive for IE both the *definite* and *possible* categories. Abbreviations as in Table 3.

months later. CIED infection did not recur in any of these patients during subsequent follow-up.

DISCUSSION

Infections of CIEDs are associated with significant morbidity and a high death rate, particularly in the presence of endovascular infection (20%) (6,20). The incremental cost for managing CIED infection has been estimated to be about $28,676 to $53,349 (21), nearly one-half of this amount being due to intensive care procedures (4). Furthermore, device-replacement procedures, which are periodically necessary for battery depletion or for upgrading, are associated with infection rates higher than those occurring after the initial implantation (3).

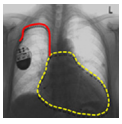
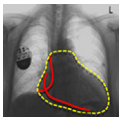
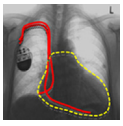
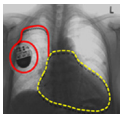
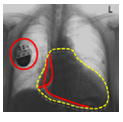
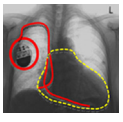
Early, definite recognition of CIED infection combined with accurate localization and quantification of disease burden could provide a rational basis for adopting optimal treatment strategies that have so far not been sufficiently defined.

In this work we evaluated a consecutive series of patients in whom the suspicion of CIED infection had been raised on clinical grounds. All patients underwent ^{99m}Tc-HMPAO-WBC scintigraphy with the purpose of validating the utility of this procedure in confirming CIED infection and in defining disease burden, the final diagnosis being obtained either by microbiology in 23 of 32 or with clinical follow-up of at least 12 months in the remaining cases.

^{99m}Tc-HMPAO-WBC scintigraphy had 94% sensitivity, and no false positive results were found, thus confirming the validity of the interpretation criteria adopted (increasing radiolabeled WBC recruitment over time at infection sites) as a diagnostic parameter enhancing specificity (16). Conversely, the 2 false negative cases of ^{99m}Tc-HMPAO-WBC scintigraphy observed in our series were most likely due to infection caused by low-WBC-recruiting microorganisms (22–24), as *Candida* and *Enterococcus* strains were isolated in the 2 patients with confirmed CIED infection in whom ^{99m}Tc-HMPAO-WBC scintigraphy was negative. Therefore, when infections sustained by such microorganisms are suspected, discontinuation of antimicrobial treatment should be considered for the enhancement of the diagnostic performances of ^{99m}Tc-HMPAO-WBC scintigraphy.

The ^{99m}Tc-HMPAO-WBC SPECT/CT images aided not only in diagnosing infection but also in defining the infection burden, in particular by distinguishing patients with infection limited to either the pocket or the lead(s) from patients with

Table 5. Results of ^{99m}Tc-HMPAO-WBC Scintigraphy, Echocardiography and Duke Criteria According to the Final Diagnosis for All the Exams Performed at Baseline, Classified According to the Site of Radiolabeled WBCs Accumulation at Scintigraphy

		Pocket Infection	Leads Infection			Pocket + Lead Infection			
CIED infections (n = 32)			Intravascular	Intracardiac	Both leads	Intravascular	Intracardiac	Both leads	Other infections
									
^{99m}Tc-HMPAO-WBC accumulation		1	1	18*†	2	2	4*	2	15
Echo	pos			14‡	2		2	2	3
	neg	1	1	8‡		2	2		12
Duke criteria	Definite			8			3		
	Possible			13			3		3
Rejected	1			2			2		12

*With concomitant IE and/or extracardiac localization for a total of 6 cases (*) and 15 cases (†). ‡Including 1 cases of FN at WBC scan. In the images the yellow line represents the heart region, the red line represents the component of the device showing radiolabelled WBCs accumulation at scintigraphy.
FN = false negative; Pos = positive; Neg = negative; other abbreviations as in Tables 2 and 3.

more severe infection involving both the pocket and the lead(s), or other sites of infection in some patients.

The intracardiac portion of the lead(s) was the site more frequently exhibiting radiolabeled WBC accumulation (n = 18); these cases were also more frequently associated with complications such as infectious endocarditis (n = 6) and/or septic embolism (n = 15). The higher prevalence of infection of the intracardiac portion of the lead(s) over the

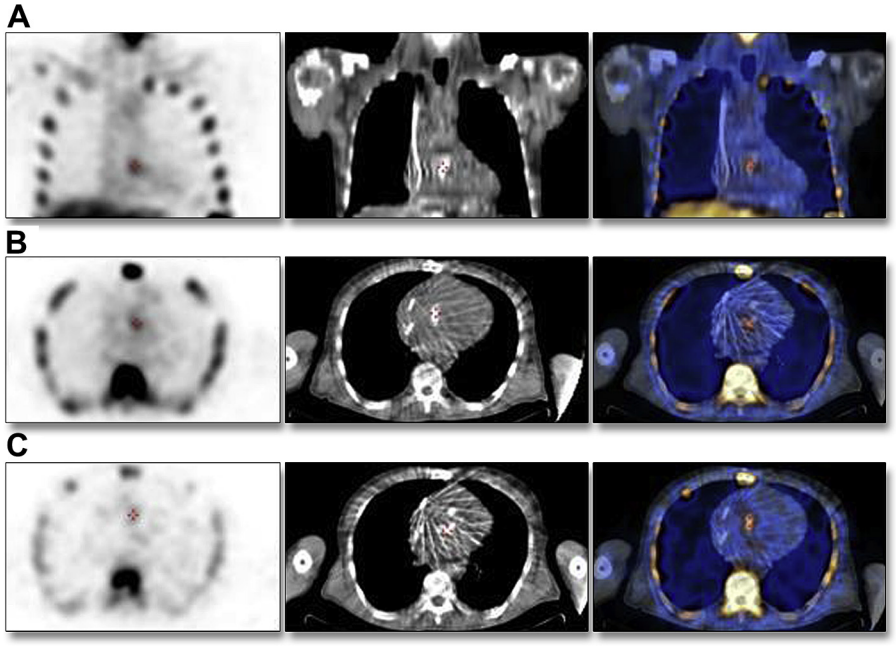


Figure 5. ^{99m}Tc-HMPAO-WBC of Suspected CIED-Related Infection at the Intracardiac Leads and Mitral Valve Mechanical Prosthesis

^{99m}Tc-HMPAO-WBC **(A)** coronal images and **(B and C)** transaxial images at different levels in a patient with CIED presenting with positive blood culture and fever 3 months after mitral valve replacement. SPECT images **(left panels)** depict focal accumulation of ^{99m}Tc-HMPAO-WBC at both the intracardiac leads **(A and B)** and the mitral valve mechanical prosthesis **(C)**. SPECT/CT images are shown in the **right panels,** and CT images, in the **middle panels**. Abbreviations as in Figure 2.

Table 6. Results on ^{99m}Tc-HMPAO-WBC Scintigraphy in Patients With Suspected CIED Infection in Whom Scintigraphy Detected Alternative Sites of Infection

Type of Infection	
Osteomyelitis*	5
Vascular graft infection	2
Mediastinitis	2
Lung infection	2
Cholecystitis	2

*Including 2 cases of spondylodiscitis.
Abbreviations as in Table 3.

surgical pocket is consistent with the relatively high prevalence of semi-late and late infections in this patient population, similar to data reported in the literature, due to slowly progressing, implant-related infection (25). Indeed, localized pocket infection was found in just 1 patient, while in all of the other cases, infection of the pocket had involvement of lead(s). An important feature of ^{99m}Tc-HMPAO-WBC scintigraphy is therefore its unique ability, shared only with PET/CT, to detect all sites of infection with a single examination, considering the frequent underestimation of the infection burden based on clinical signs alone (26).

As is standard in cases of suspected CIED-associated infection, all patients included in this study underwent echography of the cardiac region and of the venous pathway of the device as a first-line diagnostic test. In this group of patients, echocardiography had high specificity (90%), but relatively low sensitivity, for diagnosing CIED infection (63%). The echocardiographic finding of vegetations at the distal part of the lead typical for infection (27) was detected in 9 of 32 patients with confirmed infection. On the other hand, in 4 of 31 patients who were eventually classified as not having infection, a lead-associated mass, possibly of thrombotic nature, was also detected, in line with a previous report (28). Moreover, in 12 of 32 patients with a final diagnosis of CIED infection, transesophageal echocardiography failed to visualize a mass adherent to the intracardiac lead, thus confirming that a negative echocardiogram does not exclude lead infection (29). In 6 of 12 cases of negative echocardiography, ^{99m}Tc-HMPAO-WBC SPECT/CT detected infection, which was localized to the intravascular portion of the lead(s) and/or to the surgical pocket (Table 4). Therefore, when echocardiographic findings were considered in patients with intracardiac infection (n = 26), sensitivity increased to 81%.

Sensitivity of the Duke criteria was 31% in the patients classified in the *definite* category (with 100% specificity), increasing to 81% when both the *definite* and the *possible* categories were considered (with 74% specificity). This relatively low sensitivity is not surprising because the Duke criteria were originally developed for infectious endocarditis, and several of the minor Duke criteria are not applicable in this setting.

The results obtained in this study demonstrate that SPECT/CT imaging with radiolabeled WBCs in patients with suspected CIED infection increases the detection rate of infection and allows accurate assessment of disease burden. In patients with infection of a left ventricular assist device and/or valve, radiolabeled WBC SPECT/CT has been shown to determine the precise anatomic location and extension of a suspected infection, thus affecting the management of these patients (12,30). High diagnostic accuracy in patients with such a condition has been observed also with the use of PET/CT with [^{18}F]FDG, particularly for ruling out involvement of the devices during febrile episodes (31) and for defining the embolic burden in the presence of ascertained infection (32). A more recent report encourages the use of [^{18}F]FDG PET/CT also in cases of early device-related infection (10).

However, despite its high resolution, this technique is still limited by the lack of a suitable infection-specific radiopharmaceutical agent. In fact, the enhanced glucose consumption that causes increased [^{18}F]FDG uptake at infectious sites (for the presence of activated WBCs, monocyte-macrophages [33,34], and CD4^{+} T lymphocytes [35]), can also occur in a number of noninfectious, inflammatory conditions (36) and in post-surgical changes (37).

The higher specificity of ^{99m}Tc-HMPAO-WBC scintigraphy observed in our study when employing SPECT/CT imaging (with spatial resolution better than that with planar or stand-alone SPECT) enabled precise definition of the disease burden, therefore allowing risk stratification and decision making. In fact, similar to findings observed with [^{18}F]FDG PET/CT, a negative scan has consistently been associated with a favorable clinical outcome when antimicrobial therapy alone was initiated. Indeed, a negative ^{99m}Tc-HMPAO-WBC SPECT/CT might be used as a guide for clinicians in choosing the most suitable, that is, conservative, treatment (antimicrobial agents alone, or removal of only the generator) versus full hardware extraction.

Study limitations. Although WBC imaging is a relatively more complex procedure compared with [^{18}F]FDG PET/CT both in terms of radiopharmaceutical preparation, which includes blood manipulation, and imaging acquisition, which requires multiple scans at different time points, we believe that when differentiation between active infection and inflammation is crucial, ^{99m}Tc-HMPAO-WBC should be considered the method of choice.

CONCLUSIONS

^{99m}Tc-HMPAO-WBC scintigraphy with SPECT/CT acquisition of the chest in patients with a high clinical suspicion of CIED infection enabled confirmation of the presence of infection, definition of the extent of device involvement, and detection of associated complications such as infectious endocarditis and septic embolism. In addition, ^{99m}Tc-HMPAO-WBC scintigraphy was helpful for excluding the presence of device-related infection during a febrile episode and sepsis, with a 95% negative predictive value. Demonstration of the impact of functional imaging on the overall healthcare costs of the clinical management of CIED on a large scale represents the next challenge.

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Key Words: cardiac device infection ■ disease burden ■ SPECT/CT ■ ^{99m}Tc-HMPAO-WBCs.