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High diagnostic accuracy of white blood cell scintigraphy for fracture related infections: Results of a large retrospective single-center study

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ABSTRACT

Introduction: White blood cell (WBC) scintigraphy for diagnosing fracture-related infections (FRIs) has only been investigated in small patient series. Aims of this study were (1) to establish the accuracy of WBC scintigraphy for diagnosing FRIs, and (2) to investigate whether the duration of the time interval between surgery and WBC scintigraphy influences its accuracy.

Patients and methods: 192 consecutive WBC scintigraphies with ^{99m}Tc-HMPAO-labelled autologous leucocytes performed for suspected peripheral FRI were included. The golden standard was based on the outcome of microbiological investigation in case of surgery, or – when these were not available – on clinical follow-up of at least six months. The discriminative ability of the imaging modalities was quantified by several measures of diagnostic accuracy. A multivariable logistic regression analysis was performed to identify predictive variables of a false-positive or false-negative WBC scintigraphy test result.

Results: WBC scintigraphy had a sensitivity of 0.79, a specificity of 0.97, a positive predicting value of 0.91, a negative predicting value of 0.93 and a diagnostic accuracy of 0.92 for detecting an FRI in the peripheral skeleton. The duration of the interval between surgery and the WBC scintigraphy did not influence its diagnostic accuracy; neither did concomitant use of antibiotics or NSAIDs. There were 11 patients with a false-negative (FN) WBC scintigraphy, the majority of these patients (n = 9, 82%) suffered from an infected nonunion. Four patients had a false-positive (FP) WBC scintigraphy. **Conclusions:** WBC scintigraphy showed a high diagnostic accuracy (0.92) for detecting FRIs in the peripheral skeleton. Duration of the time interval between surgery for the initial injury and the WBC did not influence the results which indicate that WBC scintigraphy is accurate shortly after surgery.

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Introduction

Postoperative infection is one of the most common and yet also most severe complications associated with the surgical fixation of fractures. It results in increased morbidity, higher medical costs and prolonged hospital admission times [1,2]. Despite new and promising methods to prevent and treat these infections, the key to

successful management is to establish an early and correct diagnosis. A distinction used to be made between early and late infections. However, classifications are rather arbitrary and there is no scientific evidence that the timing of the onset of the infection has any effect on the diagnostic tests or the treatment outcome. As a result, new definitions are being developed. In a recent consensus meeting supported by the Association for the Study of Internal Fixation (*Arbeitsgemeinschaft für Osteosynthesefragen*, AO), it was agreed to refer to the complete spectrum of infections following surgical fixation of a closed or open fracture as “fracture-related infection” (FRI) when no further detailed information is available on the degree of bone involvement. Also, clear definition criteria now finally exist [3]. Many factors (both patient-related and doctor- or

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health institution-related) play a role in the clinical decision-making process for diagnosing FRI [4,5]. Usually it is not early FRIs which pose a diagnostic challenge. Clinical signs of early infections are clear and tend to be easily recognizable, requiring limited or no additional diagnostic imaging. From a diagnostic perspective it is the established form of FRI which can be difficult to diagnose, and advanced medical imaging can be indispensable. However, most studies that investigate the accuracy of these advanced imaging modalities are aimed at hematogenous osteomyelitis and prosthetic joint infections (PJIs), or are conducted in an inhomogeneous orthopedic population with infections of different etiology [6–8]. FRIs are a different entity than PJIs because fracture fixation implants are in situ, which often allows micro-motion of the surrounding bone in contrast to an articulating but otherwise rigid prosthesis. There may also be confounding factors present such as a recent fracture with regenerating bone, soft-tissue disruption and/or other concomitant injuries. In many countries white blood cell (WBC) scintigraphy is a commonly utilized imaging modality for orthopedic infections, including FRI [9,10]. However, although labeling and interpretation guidelines for WBC scintigraphy are now set by the European Association of Nuclear Medicine (EANM) [11], evidence of its accuracy in FRIs is limited in the literature [12]. There is also uncertainty regarding the minimum time interval required between surgery and WBC scintigraphy in order to minimize postoperative artifacts (and therefore false-positive results). As a FRI is a surgical complication it is important to know how previous surgery influences the outcome of any diagnostic test.

To resolve these questions, the two aims of this study were:

- 1) to establish the accuracy of WBC scintigraphy for diagnosing FRI in a large and homogeneous patient group.
- 2) to investigate whether the duration of the time interval between surgery and WBC scintigraphy influences its diagnostic accuracy.

Patients and methods

The local hospital information system was reviewed for all consecutive patients who underwent a WBC scintigraphy for suspected FRI between 1 February 2009 and 8 November 2016. FRI was defined as any bone infection resulting from the surgical or non-surgical treatment of an open or closed fracture. The index event was the date of injury for an open conservatively managed fracture and the date of the operation in case of surgery. The WBC scintigraphy had to be aimed at diagnosing or excluding an FRI in relation to the index event. Patients with other types of orthopedic infections (such as PJI, spondylodiscitis and hematogenous osteomyelitis) were excluded. Additionally, the suspected FRI had to be located in the peripheral skeleton, as 1) the upper and lower limb are the most commonly affected anatomical regions and 2) WBC scintigraphy does have limitations in imaging the axial skeleton due to the relatively high uptake of white blood cells in the liver, spleen and bone marrow, and as such may obscure the specific uptake [5,12,13].

The final diagnosis of FRI (the gold standard) was based on the outcome of medical microbiological (MMB) investigations in case of surgery, or – when these were not available – on clinical follow-up of at least six months. Judgment of validity of the MMB results was done by an experienced trauma surgeon. The microbiological results of swabs and cultures of fistulas were disregarded due to relatively low accuracy [14–16]. Only if more than two deep-tissue cultures were available from the suspected site were the MMB results accepted as relevant. If this was not the case, the final diagnosis was based on clinical follow-up. A positive MMB was defined as accurate microbiology sampling combined with at

least two positive cultures with the same organism [17,18]. A positive result at clinical follow-up was defined as any wound break down, the presence or development of a sinus tract or redness and/or swelling that prompted the clinician to start the patient on antibiotic treatment or commence surgery. If the patient had an operation because of a suspected infection due to clinical symptoms after an initially negative WBC-scan the MMB results were evaluated and taken into account in regard to the initial scan.

The electronic patient files of all included patients were retrospectively reviewed to collect all data, including demographic details, information on the use of steroids and/or antibiotics, mechanism of injury, type of fracture according to the Müller AO Classification of Fractures [19], Gustilo Anderson classification in case of an open fracture [20], microbiological results, and clinical details at follow-up. The anesthesia files were reviewed for the American Society of Anesthesiologists (ASA) classification [21], Body Mass Index (BMI), comorbidities, use of nicotine and/or recreational drugs, and use of other relevant medication.

Ethical approval

Due to the observational nature of this analysis, in accordance with Dutch law the local medical ethical committee was informed about this research project and a waiver was granted (number METc2014.395).

WBC scintigraphy, acquisition and analysis

To properly analyze the results, all WBC scans were reassessed by an experienced nuclear medicine physician who was blinded for all clinical and microbiological results. All scans in the studied timeframe were performed using the same protocol. Radiolabeling of the autologous WBC (mixed leukocytes) with ^{99m}Tc -HMPAO was performed according to current EANM guidelines [11]. In accordance with recent insights on the correct acquisition and analysis of WBC scintigraphy dual time-point acquisition was used, with static images acquired 4 h and 20–24 h after intravenous injection of 370–555 MBq ^{99m}Tc -HMPAO-labelled WBC [10,22]. The images were acquired with decay-corrected acquisition times and displayed and analyzed using a total counts intensity scale with the same intensity threshold, thus avoiding observer bias. A SPECT (40 s per frame, 360° rotation) with low-dose CT scan was performed for precise location in all patients in whom uptake was seen on the 4 h images. All scans were performed on a SPECT/CT gamma camera system (SymbiaTM T, Siemens Medical Systems, Knoxville, TN, USA). Scans were visually classified as negative for infection when 1) there was no uptake at all on both images, 2) when the uptake decreased in time, or 3) when the uptake remained the same in time. Scans were visually classified as positive for infection when the uptake showed an increase in size and/or intensity in time. In equivocal cases, semi-quantitative analysis was performed by drawing a region of interest (ROI) over the suspected infectious focus and an automatically mirrored ROI over contralateral reference tissue. The mean counts per pixel in these ROIs were recorded and a lesion-to-reference tissue (L/R) ratio was calculated on both images. When the L/R ratios decreased or remained stable in time, the scan was considered negative for infection. When the L/R ratios increased in time, the scan was considered positive for infection. Hence only the planar images were used for declaring a scan positive or negative for infection, first visually and in equivocal cases semi-quantitatively. When a scan was considered positive for infection, SPECT/CT was used to determine if the infection was located in the bone (FRI) or outside the bone (soft-tissue infection). A clinical example of a WBC-scintigraphy + SPECT/CT for diagnosing a FRI is presented in Fig. 1.

Fig. 1. Clinical example.

A 57-year-old man was treated with a plate osteosynthesis for a crural fracture (A) 10 months ago. He presented with a small area of redness and tenderness at the distal-medial tibia. WBC scintigraphy showed an increased uptake in the distal tibia in both the early and late phases (B) of the scan, with intensity increasing in time. A SPECT/CT (C) demonstrated a hotspot around the lag screw in the tibia. The patient was operated and there was an infection detected around the lag screw. All osteosynthetic materials were removed. Subsequently, the infected bone around the lag screw was debrided (D) and a cement spacer (E) was temporarily placed in a small tibial bone defect. Cultures of the implants demonstrated an *ochrobactrum intermedium* microorganism. After IV and oral treatment with antibiotics, the bone defect was filled with a cancellous bone graft during the second stage of this Masquelet procedure (F). The patient recovered uneventfully.

Statistical analysis

Either descriptive statistics (mean and standard deviation (SD) or median and range, frequency and percentages) were used to describe the characteristics of the study population. The discriminative ability of the imaging modalities was quantified by several measures of diagnostic accuracy: sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (PLR and NLR), and the diagnostic odds ratio (DOR).

To assess whether a variable was predictive of a false WBC scintigraphy test result (false-positive or false-negative versus true-positive or true-negative), a multivariable logistic regression analysis was performed. The following variables were entered into the model: duration of the interval between last surgery before WBC scintigraphy and the actual WBC scintigraphy itself, diabetes, obesity (defined as a Body Mass Index (BMI) ≥ 30 kg/m²), smoking, drug use, and NSAID treatment or antibiotic treatment at time of WBC scintigraphy. The interval between last surgery and WBC scintigraphy was categorized into 0–3 months, 3–6 months and >6 months. A backward stepwise selection procedure was used, with Akaike's information criterion ($P < 0.157$) as selection criterion. Odds ratios (OR) with 95% confidence intervals were calculated. An OR > 1 indicated that patients with a specific variable (for instance, obesity) had higher odds of having a false WBC scintigraphy test result than patients without the presence of that variable. Additionally, two similar models were constructed to assess whether the aforementioned variables were predictive of a specific false test result (false-positive versus true-positive, and false-negative versus true-negative). Statistical analyses were performed using IBM Statistics for Windows software (SPSS version 23.0, Armonk, NY: IBM Corp.).

Results

During the inclusion period a total of 192 WBC scintigraphies were performed in 162 patients who met the inclusion criteria. All WBC scintigraphies were requested for actual or suspected peripheral FRI. The patient characteristics are summarized in

Table 1
Patient characteristics (N = 162).

Sex ^a	
Male	104 (64)
Female	58 (36)
Age (years) ^b	50.4 (12.2–87.3)
BMI ^b (N = 141)	28.5 (18.2–46.3)
ASA classification ^b (N = 146)	1.8 (1–3)
I ^a	55 (38)
II ^a	68 (47)
III ^a	23 (16)
Comorbidities and other risk factors ^a	
Diabetes	23 (14)
Psychiatric disorder	14 (9)
Obesity	25 (15)
(Pre-)malignant disorder	4 (3)
Anemia	1 (1)
Hypothyroidism	6 (4)
Smoking (N = 143)	52 (36)
NSAIDs ^{***}	21 (13)
Corticosteroids	7 (5)
Recreational drugs	7 (4)
Cannabis	3 (2)
Heroin/methadone	4 (3)
Antibiotic treatment	17 (10)

*BMI: Body Mass Index, **ASA: American Society of Anaesthesiologists, ***NSAIDs: Non-Steroidal Anti-Inflammatory Drugs.

^a Data presented as N (%).

^b Data presented as mean (range).

Table 2
Fracture characteristics.

Fracture type according to Müller AO classification (N = 192) (19)		
1: Humerus		18
	11: Proximal	4
	12: Diaphyseal	4
	13: Distal	10
2: Radius/ulna		9
	21: Proximal	3
	22: Diaphyseal	6
	23: Distal	0
3: Femur		50
	31: Proximal	10
	32: Diaphyseal	27
	33: Distal	12
	34: Patella	1
4: Tibia/fibula		100
	41: Proximal	11
	42: Diaphyseal	40
	43: Distal	20
	44: Malleolar	29
8: Foot		15
Soft tissue injury (N = 192)		
	Closed Fracture	102
	Open fracture	90
Gustilo-Anderson Classification (N = 90)		
	Type 1	17
	Type 2	24
	Type 3A	27
	Type 3B	4
	Type 3C	5
	Unknown	13

*N = total number of WBC scintigraphies included for analysis.

Table 1. The fracture specifics are presented in **Table 2**, the type of index operation in **Table 3**.

In 51% of cases (77 patients with 97 WBC scintigraphies) an adequate microbiological result was available. This cohort had a mean clinical follow-up of 18.3 months (SD 15.3), and 44 patients had an MMB-confirmed infection. Staphylococci were the most commonly identified organism (**Table 4**), with MRSA in two patients. Two patients had negative cultures but they both had a clear clinical FRI with a chronic and with the implant communicating fistula. Both patients were operated on by an experienced orthopedic surgeon specialized in PJI and FRI who diagnosed the FRI based on intraoperative assessment. The WBC scintigraphies for both these patients were positive and therefore regarded as true-positive. The patients without adequate MMB results (85 patients with 95 WBC scintigraphies) had a mean clinical follow-up of 21.9 months (SD 17.1). In this group 8 additional patients had a clinically detected infection during follow-up.

Table 3
Index operation (N = 192).

Intramedullary nail		45 (23)
Plate		69 (36)
Screw(s)		7 (4)
Dynamic hip screw		7 (4)
External fixator		44 (23)
Followed by		
- Intramedullary nail	10	
- Plate	19	
- Screw(s)	2	
- Remaining cast	4	
- Remaining external fixator	3	
- Other	6	
Closed reduction		10 (5)
Managed conservatively		2 (1)
Other		3 (2)
Unknown		5 (3)

Data presented as N (%).

Table 4
Microbiological results of intraoperative collected tissue samples.

Etiology of infection	Results of 44 culture-positive patients	Results of 9 culture-positive patients with false-negative WBC
<i>Staphylococcus</i> spp.	28	6
<i>Corynebacterium</i> spp.	4	2
<i>Enterococcus</i> spp.	5	1
<i>Propionibacterium</i> spp.	5	2
<i>Streptococcus</i> spp.	3	1
<i>E. Coli</i>	3	1
<i>Pseudomonas</i> spp.	2	
<i>Actinomyces</i> spp.	1	
<i>Peptoniphilus</i> spp.	4	
<i>Klebsiella</i> spp.	2	
<i>Finnegoldia</i> spp.	1	
<i>Proteus</i> spp.	1	
<i>Dermabacter</i> spp.	1	
<i>Bacteroides</i> spp.	1	
<i>Serratia</i> spp.	1	1
Polymicrobial N (%)	14 (32)	5 (56)

Overall there were 52 cases with an FRI; the WBC scintigraphy detected this correctly 41 times (TP). There was no FRI 140 times, as confirmed by WBC scintigraphy in 136 cases (TN). Four scans were false positive (FP) and 11 scans were false negative (FN). This resulted in 0.79 sensitivity, 0.97 specificity, 0.91 PPV, 0.93 NPV, 0.92 diagnostic accuracy, 126.7 DOR, 26.3 PLR and 0.22 NLR for the WBC scintigraphy to detect an FRI in the peripheral skeleton. Multivariable logistic regression analyses showed that only obesity was predictive of a false WBC scintigraphy test result ($P = 0.008$, $OR = 5.42$). The median BMI of the 4 patients with FP results was 36.0 kg/m^2 (range 29.7–37.4), of the 11 patients with FN results 29.4 kg/m^2 (range 24.8–35.6) and of the cohort patients with true results (TP + TN) 27.7 kg/m^2 (range 18.2–46.3) respectively. The duration of the interval between the operation and the WBC scintigraphy did not influence its diagnostic accuracy. In the group of WBC-scintigraphies performed within 0–3 months after the last surgery there were 15 correct (TP + TN) and zero incorrect (FP + FN) scan results. In the group of WBC-scintigraphies performed within 3–6 months this number was 37 and five, respectively, and in the group of WBC-scintigraphies performed six months or more after the last surgery this number was 124 and 10, respectively. Median interval between last surgery and WBC-scintigraphy was 10.7 months (range 0.2–490.2). There were 9 patients with an interval of more than 10 years (median 180.0 months, range 126.1–490.2), the accuracy results of these patients were 1 TP, 6 TN and 3 FN respectively. All other variables were discarded from the logistic regression models. The additional logistic regression analyses showed that obesity was mainly predictive of a false-positive WBC scintigraphy test result ($p = 0.035$, $OR = 11.67$). The results of the multivariate logistic regression analyses are presented in Table 5.

Table 5
Results of multivariable logistic regression analyses.

Model ^a	Variable	Regression coefficient	P-value	OR (95% CI)
1. False test result vs true test result	Obesity	1.69	0.008	5.42 (1.55–19.00)
2. FP vs TP	Obesity	2.46	0.035	11.67 (1.19–114.90)
3. FN vs TN	Obesity	1.39	0.08	4.03 (0.87–18.75)

Abbreviations: FP, false-positive; TP, true-positive; FN, false-negative; TN, true-negative; OR, odds ratio; CI, confidence interval.

^a True WBC scintigraphy test result was used as reference group. No other variables are reported, as they do not constitute significant predictors of a false test result.

False-positive/false-negative patient characteristics

There were 11 patients with a false-negative (FN) WBC scintigraphy. Nine patients had positive MMB results, the other two were detected during clinical follow-up. Nine of the 11 FN patients had low-grade infected nonunions of bones in different body regions. The radius and ulna were involved in one case, the femur in two cases, the tibia in five cases, and the fibula in one case. One 45-year-old man with an FN result presented with an erysipelas which eventually turned out to be a chronic FRI of the tibia 24 years after a fracture (initial treatment involved an external fixator). The last patient with an FN result presented with a non-healing wound at the lower leg due to a long-standing FRI of the fibula 70 years after a grenade injury. His interval between last surgery and WBC scintigraphy was over 37 years. Overall all the majority of patients with a false negative WBC scintigraphy ($N = 9$, 82%) in these series had low-grade infected non-unions.

Four patients had a false-positive WBC scintigraphy. One of them was a 45-year-old female who was treated for a nonunion at one year after a grade-1 complicated femoral fracture that was initially treated with an intramedullary nail. At revision surgery the cultures turned out to be negative despite a positive WBC scintigraphy. The second patient with an FP result was a 40-year-old female with a grade-3A complicated femoral fracture for which she was operated several times. She had a 12-cm bone defect and cancellous bone graft in situ, and was treated for a nonunion two years after the initial injury. The third patient with an FP result was a 35-year-old man who was treated for a nonunion of the tibia three years after a complicated lower extremity fracture. The last patient with an FP result was a 73-year-old woman who had a nonunion of the distal femur one year after a complicated femoral fracture that was initially treated with a plate osteosynthesis.

Discussion

Based on the results of a large patient cohort, we report a high diagnostic accuracy (0.92) of WBC scintigraphy for FRI in the peripheral skeleton with a sensitivity of 0.79, a specificity of 0.97, a PPV of 0.91, and an NPV of 0.93. We found no difference in accuracy of previously performed WBC scintigraphies (between 0 and 3 months after surgery) compared to subsequent scans.

Nuclear imaging is evolving rapidly; therefore only recent studies can be compared with current practice. Since the turn of the millennium five comparable studies have been published on the accuracy of WBC scintigraphy for FRI. Only two of these studies utilize SPECT/CT as an adjunct to WBC scintigraphy in case of a positive result. This has shown to improve diagnostic accuracy, as it distinguishes whether the infection is situated in the bone or in soft tissue [10,12,23]. The specificity in our study is in line with the aforementioned studies investigating WBC scintigraphy in combination with SPECT/CT, yet the sensitivity in our study is lower. The reason is unclear even though the inclusion criteria in the two other studies are similar to ours. However, the strength of the current study is that it consists of a much larger consecutive series (our study consists of 192 WBC scintigraphies vs 49 [10] and 29 [23] WBC scintigraphies respectively).

Whether an imaging result can be trusted shortly after an operation or fracture, is important for a correct interpretation of the results. Especially regenerating bone and soft-tissue disruption is expected to have some impact on the results of a WBC scintigraphy, probably similarly to a bone scan, magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET) scan [5,12]. In our study the only variable highly predictive for a false result was obesity. The reason for it is unknown and this phenomenon has not been reported earlier in the literature. We should however keep in mind that this result is based on a limited number of FN (N = 11) and FP (N = 4) patients with the highest BMI in the group with FP results. Further prospective research is warranted to explain these findings. None of the other variables influenced the results of the WBC scintigraphy (Table 5). This means that a WBC scintigraphy is not only accurate shortly after an operation, but also with the concomitant use of recreational drugs, antibiotic treatment, smoking or comorbidities such as diabetes mellitus.

The limitations of this study, apart from its retrospective design, include the potential for selection bias as usually only patients with clinically difficult-to-detect FRIs undergo advanced nuclear imaging. It was not feasible to identify all patients with a low-grade FRI, but when we analyzed the FP and FN WBC scintigraphies we detected that nine out of the 11 patients with an FN scan result had the clinical appearance of a low-grade infected nonunion. One could argue that WBC scintigraphy might be less accurate in low-grade FRI due to lower leucocyte availability (hence the lower sensitivity). Unfortunately, this may be the patient population for whom a WBC scintigraphy is usually requested, therefore further prospective studies that include other imaging modalities such as MRI and FDG-PET are warranted.

Conclusion

In conclusion, this study indicates:

- 1) That WBC scintigraphy has a high diagnostic accuracy (0.92) for detecting fracture-related infections in the peripheral skeleton based – for the first time – on a large patient cohort.
- 2) That the time interval between WBC scintigraphy and previous surgery does not interfere with the results. This means that a WBC scintigraphy is accurate shortly after an operation.

Source of funding

No external funds were received in support of this study.

Conflict of interest

This manuscript, including related data, figures and tables has not been previously published and is not under consideration by another journal. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication. Each author has made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content. Each author read and approved the manuscript and believes that the manuscript represents honest work.

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