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MAJOR ARTICLE

Lack of Clinical Utility of Labeled White Blood Cell Scintigraphy in Patients With Fever of Unknown Origin

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Background. Labeled white blood cell scintigraphy (WBCS) has been used for over 40 years to localize an infection source in patients with fever of unknown origin (FUO). It continues to be in widespread use for such patients in modern times, despite the tremendous advances in modern radiological imaging and laboratory medicine.

Methods. We critically evaluated the clinical contribution of WBCS performed in 132 patients with FUO at 7 hospitals from mid-2015 to the end of 2019. For each patient, all radiographic and laboratory results and all electronic clinical notes were carefully evaluated as many days before and after the scan as necessary to arrive at a final diagnosis.

Results. Although 50 WBCS (38%) showed positive findings, the majority of these were false positive (FP). Of the 19 true-positive (TP) scans, most were already known or about to become known by tests already ordered at the time of the scan. Only 2 TP scans (1.5%) contributed to the final diagnosis, and these did so only indirectly. FP scans led to 7 unnecessary procedures.

Conclusions. In FUO patients for whom an infection source is not discovered following an appropriate radiographic and laboratory workup, WBCS is not a useful procedure.

Keywords. scintigraphy; leukocyte; fever; unknown; origin.

The definition of fever of unknown origin (FUO) has evolved over time but typically refers to persistent fever that remains undiagnosed following a reasonable evaluation, usually consisting of at least 3 days of hospital evaluation or 3 outpatient visits, with a duration of >3 weeks [1–3]. If the conventional workup, which includes laboratory and standard radiological evaluation, is negative, it can be very challenging to find the source—thus, a whole-body scan that sensitively detects infection/inflammation is highly desirable. Radiolabeled white blood cell scintigraphy (WBCS) is a technique in which a patient's own leukocytes are labeled with a radioactive tracer, indium-111 or technetium-99m [4]. The reinjected white cells migrate to sites of infection by chemotaxis. Subsequent whole-body scanning shows the distribution of these white cells in areas of infection or noninfectious inflammation [5].

When WBCS was introduced clinically in the 1970s [6], it was a tremendous advance for the imaging of infection. Computed tomography and magnetic resonance imaging (MRI) were not yet available, and for the first time, large abscesses, which had previously been invisible, could be diagnosed and localized. But beginning in the mid-1980s, computed tomography (CT) and then MRI became available, providing much better tools for diagnosing infections. WBCS persists today for a few indications, including evaluation of the patient with FUO [7]. In this study, we question whether WBCS, although still widely recommended and ordered [8–11], is truly useful for patients with FUO.

Imaging for FUO

Conventional imaging in these patients typically includes chest x-ray and/or chest/abdomen CT [12]. MRI may be used if there are specific areas of clinical suspicion, such as the spine or central nervous system [3]. WBC scintigraphy is most often used when conventional imaging and laboratory tests have not localized the infection source. In many cases, it is a "last resort" technique to exclude an occult infection.

METHODS

Patient Consent

None of the authors have any conflicts of interest, financial or otherwise, with regards to this study. No patient consent was obtained, as this study involved a retrospective analysis of the electronic medical record. The Houston Methodist Research Institute IRB waived the need for IRB approval, based on the

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fact that this project involved quality control and patient safety, and also due to the retrospective nature of the study.

All WBCS were performed in the Houston Methodist Hospital system (a 1200-bed mixed academic/private practice hospital in the Texas Medical Center, plus 6 community private practice Methodist hospitals in Houston). Eighty percent of the studies were performed in the medical center hospital. All studies were performed by obtaining ~50 cc of the patient's blood and sending it to an off-site lab, where the white cells were removed by centrifugation and labeled with 0.5 mCi (18 MBq) of indium-111-oxine (115 patients) or 10 mCi (370 MBq) of Tc-99m-HMPAO (17 patients). The labeled white cells were resuspended in the patient's plasma and sent back to our hospital for immediate reinjection into the patient. Scanning was performed 24 hours later (indium-111) or 2–3 hours later (Tc-99m), as per standard nuclear medicine protocols [13]. Whole-body imaging was performed on a total of 16 Siemens and GE dual-headed scanners at 7 hospitals, at a rate of 6 cm/min (~30-minute scan time). Medium-energy collimators were used for In-111 imaging, low-energy all-purpose collimators for Tc-99m. SPECT-CT was available at only 1 hospital and was performed on 4 patients, as requested by the nuclear medicine physician after viewing the whole-body scan, but did not change the interpretation in these cases. Methodist IRB waived full review as the study was conducted primarily as a quality improvement project and due to the retrospective, chart-review nature of the study.

Cases were selected using software purchased from Montage-Nuance (Nuance Communications, Burlington, MA, USA). The radiology database for all 7 hospitals was searched for WBC scans with the indication "fever of unknown origin" or "sepsis of unknown origin" from November 2015 (the start of the Montage database) to the end of 2019. 2020 was not included, as it was not known if the COVID-19 pandemic would produce unusual WBCS results. The patient was used in the study only if the provided indication could be confirmed using the Epic electronic medical record. This yielded 132 adult patients, ages 25–83, median age 61. Each patient had 1 scan. Most patients were inpatients (91%). Original clinical interpretations were performed by 1 of 3 board-certified nuclear medicine physicians, each of whom has >10 years of clinical nuclear medicine experience. These original interpretations were used as the scan results. For each case, the WBCS images and all other radiographic images were reviewed further by 1 or both of the nuclear physicians in this study (R.F. or E.P.) in order to accurately determine if the scan results were TP, FP, etc. Using Epic and our PACS (GE Healthcare), we determined whether any positive or negative WBCS findings were confirmed as correct and useful, as discussed below. All relevant electronic clinical notes as many days before and after the scan as necessary, along with all relevant pathology and imaging reports, were carefully scrutinized. The final FUO diagnosis was determined by the notes of the infectious disease consultant or, if there was no consultant, by the internist taking care of the patient.

For every positive finding on WBCS, we addressed the following questions:

1. Was the finding confidently confirmed by pathology or other imaging? We did not accept as TP the scenario in which clinicians considered the finding on WBCS to be the cause of fever without corroborative evidence.
2. Was the finding already known (or about to become known) from another test result? If so, even a TP added nothing and was not clinically useful.
3. If a chest or abdomen CT had been performed instead of WBCS, would the same diagnosis have been made? This question could be answered in most cases, as CT was usually performed after a positive WBCS result.

RESULTS

Of 132 patients, 50 scans (38%) showed positive findings, and 82 scans were negative.

Positive Scans

Of these 50 positive cases, 19 (38%, or 14% of all scans) showed positive scan findings that could be confirmed as true positives. However, careful evaluation of the electronic records of these 19 TP cases showed that 17 were not clinically helpful:

- Ten were already known or became known shortly after scan by tests not ordered because of scan findings. Thus, these findings would have been known even if the WBC scan had never been ordered. Etiologies include *C. difficile* colitis (Figure 1A), pneumonia (6 cases, eg, Figure 1B), cellulitis, sinusitis, and gangrene.
- Two were deemed clinically unimportant and were ignored; these did not change management of the patient.
- Three would have been diagnosed as well or better by a chest CT that had not yet been ordered (pneumonia).
- Two were somewhat helpful, but with limitations, as discussed below.

Two TP Cases Were Somewhat Helpful

Patient #102: The patient required mechanical ventilation, with a chest x-ray (CXR) showing left lower lobe (LLL) infiltrate (Figure 2A). The patient received empiric antibiotics, but the fever persisted. WBCS showed focal pneumonia, but already seen on CXR and seen 3 days later on CT. Sputum grew the fungus *Curvularia*. The pulmonary consultant determined that, based on the *Curvularia* culture combined with WBCS and CXR results, bronchoscopy was indicated. Bronchoalveolar lavage grew a variety of molds/fungi, and antifungal medication was added. The patient, however, failed to improve, and 5 days later a CT of the sinuses was performed, which revealed an aggressive-appearing sinusitis

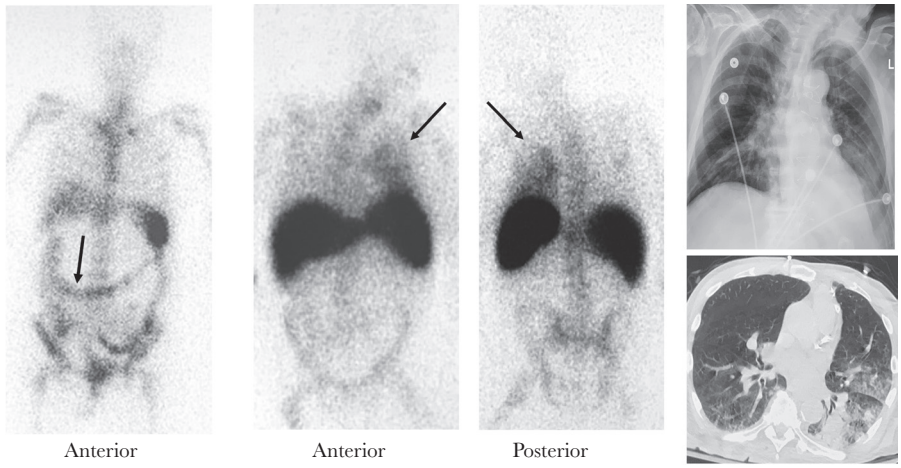


Figure 1. Examples of TP, but not helpful, scans. A, *C. diff* colitis. WBCS—note prominent uptake throughout nearly the entire colon. *C. diff* labs had been requested 3 days before the scan but were delayed, and results came back a few hours after imaging. B (top), Pneumonia. Anterior and posterior images of WBCS showing large LLL pneumonia. CXR (upper right) showed this 24 hours earlier, and CT (bottom right) showed it 3 days later. Respiratory cultures came back (+) for MRSA 1 day after WBCS. The scan was requested primarily to exclude additional sources of infection. Abbreviations: ANT, anterior; *C. diff, Clostridioides difficile*; CT, computed tomography; CXR, chest x-ray; LLL, left lower lobe; MRSA, methicillin-resistant *Staphylococcus aureus*; POST, posterior; TP, true-positive; WBCS, white blood cell scintigraphy.

with bone erosion. The patient was promptly taken to the OR for sinus debridement. The WBCS was false negative (FN) for the most important infection—sinusitis (compare to Figure 2B). The WBCS seemed to help encourage the bronchoscopy, which eventually led to the diagnosis of fungal sinusitis. So, even though a CXR and later a CT also showed the pneumonia, we considered the scan result somewhat helpful, indirectly.

Patient #44: WBCS showed mild pelvic uptake that supported an equivocal MRI finding that had suggested osteomyelitis.

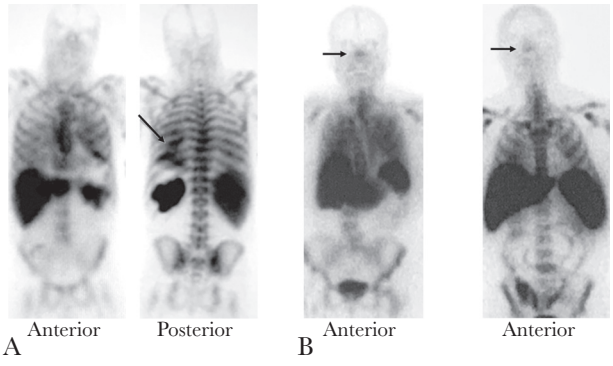


Figure 2. TP and FN, same patient. A, Tc-99m-WBCS shows LLL pneumonia (arrow, posterior view), but was already seen on previous CXR and 3 days later on CT. Sputum culture grew *Curvularia* the day before. Bronchoscopy 2 days later; washings grew a variety of mold and fungi. This led to CT sinus (patient uncommunicative) showing aggressive pan-sinusitis with bone erosion. Biopsy showed fungi and necrosis; patient was taken for surgical debridement. WBCS was FN for sinusitis. Slight prominence around orbits, nose, ethmoid sinuses is common on Tc-99m-WBCS, more so than on In-111-WBCS. B, For comparison, see examples of Tc-99m-WBCS in 2 other patients, both without sinusitis, anterior views only. Abbreviations: CT, computed tomography; CXR, chest x-ray; FN, false-negative; LLL, left lower lobe; TP, true-positive; WBCS, white blood cell scintigraphy.

False-Positive Scans

Thirty-one of our 50 positive scans (62%) were FP and included:

- Diffuse pulmonary uptake (8)—see "Discussion"
- Sinuses (5)
- Peripheral intravenous (IV) lines (4)
- Mild, nonspecific bowel uptake (3)
- Focal or diffuse bone marrow uptake (2)
- Minimal diffuse uptake in a single lung (2)
- Postsurgical inflammation from liver transplant, deemed clinically insignificant
- Benign anatomical normal variant in liver
- Recent neck biopsy
- Known malignant mass
- Cirrhotic liver
- Uninfected orthopedic hardware
- Indistinct pelvic soft tissue uptake

Five FP Cases Led to 7 Unnecessary Procedures

Patients #120 and #130: Patients' midline catheters showed mild uptake and were pulled. Both catheters were used for injection of tracer and were not infected (Figure 3). In addition, patient #130 also had FP faint uptake in the pelvis, leading to an unnecessary, negative MRI of the hips.

Patient #24: WBCS showed slight uptake near sacroiliac (SI) joints, interpreted as probably adjacent bowel, nonspecific inflammation. But the WBCS led to a pelvis MRI, which was negative.

Patient #94: Prominent bone marrow uptake of uncertain etiology led to unnecessary marrow biopsy. In retrospect, this was most likely secondary to chronic anemia.

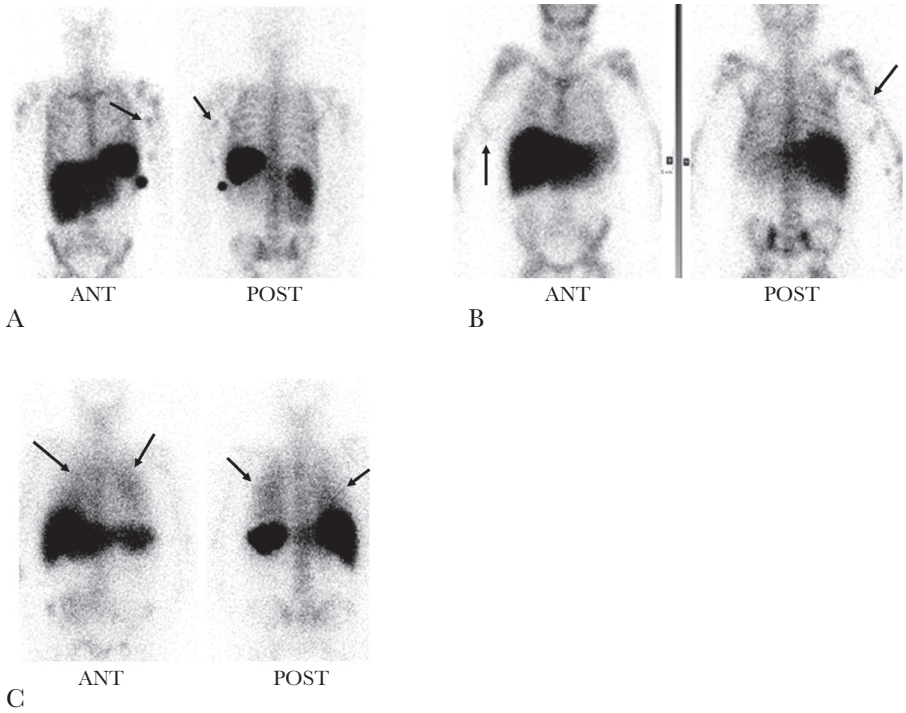


Figure 3. Examples of FP studies. A, Heart transplant patient. L midline catheter (arrow) placed 3 weeks earlier, but IV access was limited. The midline appeared uninfected clinically, and fever resolved on the day of the scan. Because of this scan, however, the midline was removed and the patient discharged. Five days later, the patient was re-admitted with identical presentation (SOB and fever). The L midline catheter uptake on this scan was very likely an artifact, as it was used for injection of tracer and certainly was not the cause of the fever/SOB. B, R midline catheter placed 24 hours after fever and elevated white count began. Midline shows prominent uptake but was used for tracer injection. C, Diffuse, prominent, bilateral lung uptake on In-111-WBCS in a febrile patient without respiratory symptoms (arrows). CT 1 day prior showed clear lungs and a 3.5-cm subcarinal LN, which was negative on this WBCS. Before the WBCS, it was decided to pursue bronchoscopy to biopsy LN: Lungs and sputum were completely negative, but LN biopsy showed tuberculosis. Bone marrow cultures later grew Tb, but there was never any clinical or lab evidence for pulmonary Tb. Final dx: reactivation of Tb in the setting of immunocompromise from recent renal tx. (Note: Mild right pelvic kidney uptake is normal in a recent tx.) Without careful review of full electronic medical records, this would have been incorrectly counted as a TP, given the discharge diagnosis of Tb. Eleven other patients in this study had diffuse lung uptake, only 2 of whom had CT evidence of diffuse pneumonia. Abbreviations: CT, computed tomography; FP, false-positive; IV, intravenous; LN, lymph node; SOB, shortness of breath; Tb, tuberculosis; TP, true-positive; tx, therapy; WBCS, white blood cell scintigraphy.

Patient #79: In-WBCS showed diffuse pulmonary uptake, interpreted as possible bilateral pneumonia. A chest CT 2 days earlier showed atelectasis vs pneumonia in the lung bases. The pulmonary consultant then performed bronchoscopy, although the patient had no pulmonary symptoms, which was unrevealing. This scan also showed mild uptake in a left pelvic transplant kidney, correctly interpreted as usually a normal finding in a transplant kidney. But the nephrology consultant was concerned about the uptake and biopsied the kidney, which showed no signs of infection or inflammation. This WBCS led to an unhelpful bronchoscopy and an unnecessary renal biopsy.

Special Cases: Sinusitis and Peripheral IV Line Infections

No useful results were found in the sinuses, with both FP and FN being common, even in the same patient (Figure 4). We had 5 FPs, 2 FNs, and our only TP was already known from a recent CT. IV line uptake was FP in all 4 cases, presumably caused by injected labeled WBCs adhering to the tubing. Two examples are shown in Figure 3.

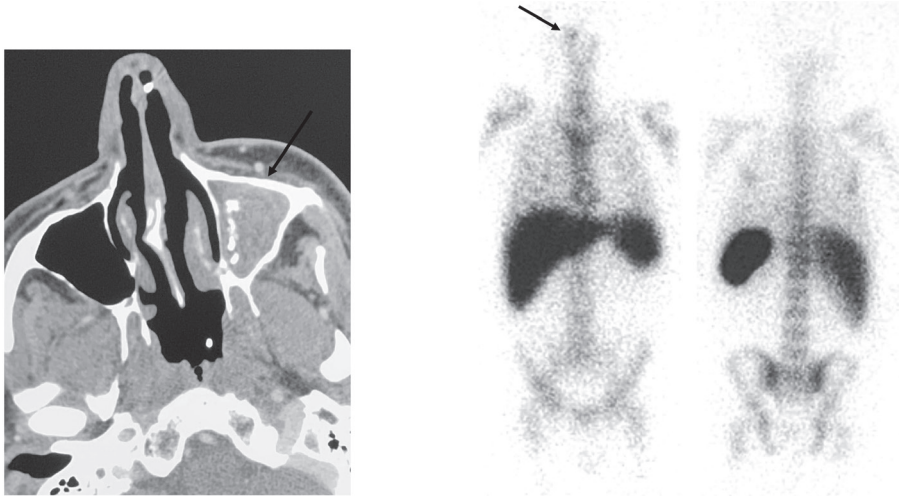
False-Negative Scans

There were 9 clearly FN scans:

- Patient with sore shoulder and fever a few days after shoulder surgery. Faint shoulder uptake was consistent with minimal postsurgical inflammation. Biopsy removed pus.
- Enlarged lymph node had been seen on prior CT, negative on WBCS. Biopsy showed infection (*Actinomyces*) in 1, lymphoma in the other (2 patients).
- Severe fungal sinusitis (2 patients)
- Port infection
- SI joint infection
- Endocarditis (echocardiography not done until after WBCS)
- Pneumonia (bilateral, but near lung bases—obscured by liver/spleen activity on WBCS)

Additional Results

In addition to classic FUO, particular subsets of these patients are often included. Our subjects could be divided into: classic



A B

Figure 4. FP and FN in the same patient. Patient on ventilator, unable to communicate. A, Sinus CT on the day of tracer injection for WBCS showed severe maxillary sinusitis (arrow), suggesting fungal infection, on the left side, perfectly normal on right. B, WBCS shows mild uptake focally on right side (arrow), unremarkable on the left. Thus, the WBCS was FP on the right side and FN on the left. ENT drained the left maxilla a few days later, which showed a mixed bacterial/fungal infection. Abbreviations: CT, computed tomography; ENT, ear, nose, and throat specialist; FP, false-positive; FN, false-negative; WBCS, white blood cell scintigraphy.

FUO (101 patients, 77%); nosocomial (7 patients, 5%); HIV-related (5 patients; 4%); and neutropenic/immunodeficient (19 patients, 14%). The etiologies of FUO are often divided into 4 major categories. Final diagnoses in our patients were infection (26%), noninfectious/inflammatory (14%), malignancy (3%), miscellaneous (3%), and no diagnosis (54%).

DISCUSSION

In the early, successful days of WBC imaging, CT and MR were not widely available, or not available at all. At present, cross-sectional imaging is a standard early evaluation for most disease processes, and the true value of WBCS now lies in what it can detect in addition to CT and MR imaging: Finding disease that could be detected on CT does not add anything to patient care.

In patients with FUO, WBCS is usually ordered after an extensive laboratory and imaging workup has failed to find the source [12]. If the source has eluded detection at this point in the workup, there is a fairly high probability that it will never be discovered [14–16]. Our results support this contention: Only 1.5% of WBCS helped discover a fever source, and only indirectly and partially. Not one by itself revealed the unknown source. Thus, the contribution to finding an occult fever source was negligible. About one-third of our WBCSs were positive (50/132). But of these, most were FP (31 scans). We did have 19 TP scans (14% of all scans), but TP results were rarely helpful, as follows.

Most TP Scans Were Not Clinically Helpful

Many studies assume that TP scans are automatically useful, but that is incorrect. In our series, TP scans usually revealed findings already known or about to be known from other imaging studies or lab tests ordered before the WBCS result. Of 19 TP scans, only 2 were clinically helpful, and in those cases contributed only indirectly or partially to the final diagnosis. This is a very small number: 1.5% of all scans, and this is offset by the fact that the FPs can mislead clinicians and lead to unnecessary procedures, as discussed below. Not a single WBCS identified a completely unsuspected infection source. The days of WBCS discovering a 10-cm abdominal abscess are gone.

FP Scans

Thirty-one of our 50 positive scans (62%) were FP. These led to 7 unnecessary procedures, including 2 biopsies. This represents a significant detriment to patient care, especially in light of only 2 TP scans being helpful, and those only indirectly.

Diffuse Pulmonary Uptake

Some of our FP scans were diffuse bilateral lung uptake on In-111-WBCS (it is a normal finding on Tc-99m-WBCS). Classifying diffuse lung uptake as false positive is debatable, as ~90% are not sites of infection [17, 18], which our study confirmed (Figure 3C). We classified 10 of our 12 cases of diffuse lung uptake as FP, as the uptake was prominent enough to be interpreted as possible infection/inflammation. Two were TP, confirmed by CT scans performed a few hours before the WBCS: 1 CT showing miliary Tb and the other showing scattered bilateral infiltrates. In both TP cases, the WBCS contributed nothing clinically.

Pneumonia Should Be Diagnosed With Chest CT, Not WBCS

Chest x-ray or CT is better, cheaper, and faster for diagnosing pneumonia than WBCS. Although there are occasional CT

scans in which it is difficult to distinguish atelectasis from pneumonia [2], this is nearly always in the lung bases, an area obscured on WBCS by high physiological uptake in the adjacent liver and spleen.

Sinusitis and IV Line Infections Are Not Well Diagnosed by WBCS

If WBCS could accurately diagnose or exclude sinusitis, this would be a small but significant contribution to the evaluation of patients with FUO. Unfortunately, we found sinus uptake to be mild, highly variable, and completely nonspecific. Both FPs and FNs were common. In fact, 1 patient was FP on 1 side and FN on the other (Figure 4). The reason for the poor performance is partly a variable normal appearance. Severe sinusitis can be fungal, as it was in our 2 FN patients, but neutrophils migrate readily by chemotaxis to most fungal infections [19]—and would thus be expected to provide a detectable signal on WBCS. Previously reported success in diagnosing sinusitis was rarely confirmed pathologically [20].

Existing peripheral IV lines are often used for injection of the labeled WBCs; this makes the significance of tracer uptake in the lines inherently equivocal, as the WBCs may occasionally adhere to the interior of the tubing. Although not widely discussed in the literature, we found several patients in whom this almost certainly occurred, all of which were in midline catheters. In fact, our results suggest that this artifact is the usual cause of peripheral intravenous line uptake, rather than chemotactic migration of labeled white cells to an infected line (which we did not observe).

The Negative Predictive Value Illusion

As WBCS is usually performed in FUO patients as a "last resort," a negative scan is often reported to be the most useful result, due to its high NPV [15, 16, 21]. A negative scan result does indeed have a high NPV in these patients, but only because at this point in the workup a fever source is unlikely to ever be found: The NPV of the WBCS is, in fact, virtually identical to the NPV of the conventional workup. A coin flip (eg, "tails" = negative) would have exactly the same high NPV too. This important point is not easily appreciated. To make it clearer: The NPV in our study was 89%. But if the WBCS had never been ordered on any of our patients, the NPV of the negative conventional workup would have been a virtually identical 88%, with a slightly less confident diagnosis in 1 case and perhaps a slightly delayed diagnosis in another. The appropriate conclusion is that the WBCS should not be ordered in these patients.

Patients With a Suspected Site of Infection

We agree with Lewis et al. that WBCS is more likely to be useful if there already exists an anatomic site suspicious for infection [16]. In many cases, these are not FUO patients by strict criteria. This contention is inferentially supported in other reports [14, 15]. Our series contained too few such cases to address this issue.

Disadvantages of WBC Scintigraphy Compared With Conventional Imaging

The leukocytes that are removed from the patient, labeled, and reinjected are known to receive a very high radiation dose [22], associated with a large number of mutations and chromosomal aberrations, with highest concern for the lymphocytes [23]. In 2003, a leading, comprehensive textbook of nuclear medicine commented, "Whether these transformed lymphocytes proliferate into a malignant process is unknown" [24]. No long-term follow-up studies were ever performed, and the issue was never resolved. Furthermore, WBCS is among the most expensive diagnostic radiology studies in modern times. In fact, our hospitals must pay an outside radiopharmacy $1495 to label the patient's white cells with indium-111 for each WBCS (Houston Methodist Hospital, 2021), compared with $150 to purchase a dose of 18-FDG for a PET scan. Finally, WBCS is a time-consuming procedure usually requiring 2 days, and imaging can take up to 1 hour. By contrast, CT imaging can often be scheduled the same day requested, and scanning of the chest, abdomen, and pelvis takes <10 minutes.

Alternatives to WBCS for FUO

There has been increasing interest recently regarding FDG PET-CT for imaging infections [25] [26], including enthusiastic publications regarding its application to FUO [27]. When the 2 techniques were compared directly or indirectly in a relatively small number of patients with FUO, FDG PET-CT outperformed WBCS [28, 29]. This was mainly because FDG PET-CT detected some malignancies, spinal infections (for which WBCS is insensitive for unknown reasons [30, 31]), and large vessel vasculitis. Most of the findings detected on PET can also be seen on conventional imaging with CT or, if focal symptoms, with MRI [32]. We are particularly concerned about increased FPs, which have always been a drawback of FDG PET [33, 34]. But most importantly, we have found that the usefulness of FDG PET or any other new imaging modality for FUO can be assessed accurately only by answering the following questions for each scan finding:

1) Was this finding also seen on conventional imaging, or would it have been if conventional imaging had been ordered?
2) Was this finding already known or about to be known by other lab tests already ordered?
3) Was the finding confirmed by other means to be the true source of fever?

We hope that future investigations of FDG PET for FUO will address these specific questions.

Limitations

A limitation of our study, and most imaging studies on patients with FUO, revolves around the nebulousness of the definition

of FUO. Strict definitions generally require at least 3 weeks of fever. In clinical practice, however, clinicians will not withhold ordering a WBCS until 3 weeks. However, this is also our study's strength, as we studied WBCS as it is used in modern clinical practice: ordered by a clinician suspecting an occult infection. Another limitation is that all studies were performed in the same hospital system in a single part of the country, although it did include 7 hospitals ranging from a large academic hospital to small- and medium-sized suburban private practice hospitals.

CONCLUSIONS

White blood cell scintigraphy for FUO is not clinically useful, can lead to unnecessary procedures, and should be avoided. The standard workup of FUO, if it includes chest CT and, depending on clinical suspicion, abdomen CT or spine/extremity MRI, is sufficient. If those imaging studies are negative, white blood cell scintigraphy adds nothing and may lead to unnecessary procedures.

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