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# Tc-99m-HMPAO White Blood Cell Scan for Diagnosis of Acute Appendicitis in Patients With Equivocal Clinical Presentation

Eric B. Rypins, M.D., F.A.C.S.,*,† David G. Evans, M.D.,*,‡ William Hinrichs, M.D.,*,§ and Samuel L. Kipper, M.D.*,‡

*From the Departments of Imaging, Emergency Medicine, and Surgery,* Tri-City Medical Center, Oceanside, California; the Department of Surgery,† University of California, Irvine, California; and the Departments of Radiology‡ and Emergency Medicine,§ University of California, San Diego, California*

### Objective
The authors' goal was to evaluate the accuracy of Technetium 99m-HMPAO-labeled leukocyte imaging for screening patients with atypically presenting appendicitis and to determine how availability of this test affected practice patterns of surgeons at the authors' medical center.

### Summary Background Data
Appendicitis can be difficult to diagnose and in equivocal cases usually requires inpatient observation. The delay may increase morbidity and costs. A test that rules out acute appendicitis could be cost effective if it allowed early discharge from the emergency department. Previously, there have been no simple, rapid, accurate noninvasive methods for improving diagnostic accuracy in patients with equivocal presentations of appendicitis.

### Methods
Patients referred to rule out appendicitis were analyzed. Patients were imaged up to 3 hours after injection of 10-mCi $^{99m}$Tc-HMPAO-labeled autologous leukocytes (Tc-WBC), and when the scans became positive, imaging was terminated and the requesting physician notified of the results. Diagnostic accuracy was established by surgical and histopathologic findings or by absence of symptoms after 1 month clinical follow-up. The source of referral, hospital length of stay, disposition of patients, and ancillary tests (ultrasound, computed tomographic scan, and barium enema) were analyzed.

### Results
One hundred twenty-four patients were studied from November 1991 through December 1995. Fifty-eight percent of positive scans showed uptake within 1 hour of injection and 73% by 2 hours. The Tc-WBC scan correctly identified an inflammatory source of abdominal pain in 65 of 66 cases (sensitivity = 98%) and was correctly negative in 55 of 58 cases (specificity = 95%). The scan correctly diagnosed appendicitis in 50 of 51 cases (sensitivity = 98%) and correctly excluded appendicitis in 62 of 73 cases (specificity = 85%). Outpatient referrals increased from 38% to 87%. In those patients with negative

scans, inpatient observation, number of adjunctive tests, and length of stay decreased significantly.

**Conclusions**

The high sensitivity and negative predictive value of Tc-WBC imaging may permit patients to be screened and discharged from the emergency department. Focally positive scans often indicate disease requiring operation but not in all cases. The Tc-WBC imaging reduced the negative laparotomy rate to 3.9% while reducing admission rates and hospital length of stay.

Acute appendicitis occurs in 7% of the Western population and approximately 200,000 appendectomies are performed in the United States each year. Accurate and timely diagnosis can be clinically challenging, making it one of the most commonly missed problems in the emergency department.[1] The consequences of missing appendicitis are increased morbidity from abscess and peritonitis, tubal infertility, prolonged hospitalization, and patient dissatisfaction with legal action against hospitals, physicians, and surgeons.[2,3]

In patients with an atypical clinical presentation or where the risk of missing the diagnosis is high, such as in pregnancy, many authorities have recommended adjunctive imaging studies. Moreover, it recently has been shown that the routine use of adjunctive tests (barium enema [BE], computed tomographic [CT] scan, and ultrasound) does not improve the overall diagnostic accuracy for acute appendicitis nor affect clinical outcomes.[4]

Technetium 99m ($^{99m}$Tc)-HMPAO (Ceretec; Medi-Physics, Amersham Healthcare, Arlington Heights, IL) is an agent that complexes avidly with polymorphonuclear leukocytes and has superior imaging qualities to indium 111, the established radioisotope used for labeling WBCs. The Tc-WBC scan provides improved image resolution, higher count rates, lower radiation exposure, and rapid uptake into areas of acute inflammation.[5,6] The Tc-WBC imaging has been approved by the Food and Drug Administration for detection of infection and inflammation. We tested the hypothesis that Tc-WBC imaging could be used to rule out appendicitis in patients presenting with lower abdominal pain and otherwise equivocal medical history, physical examination results, or laboratory values. We also determined the effect of this test on the practice patterns of emergency department physicians and surgeons in a busy community hospital regarding the diagnosis and management of appendicitis.

## MATERIALS AND METHODS

### Study Design and Selection Criteria

The study design was a prospective, consecutive trial conducted over a 4-year period from November 1991 through December 1995. The inclusion criteria consisted of acute right lower quadrant abdominal pain with an equivocal clinical presentation for acute appendicitis as determined by the referring physician or surgeon, leukocyte count of >3000 (for cell labeling), and second half of pregnancy for pregnant females. The patients were referred to the Nuclear Medicine Department for Tc-WBC imaging and designated by the referring physician as "rule out appendicitis." Referral sources included the emergency department, inpatient wards of Tri-City Medical Center, and physician's outpatient offices.

### Methods

Autologous mixed leukocytes were isolated and radiolabeled with $^{99m}$Tc hexamethylpropyleneamine oxime (Ceretec; Medi-Physics, Amersham Healthcare, Arlington Heights, IL). Forty to fifty milliliters venous blood was drawn into a 60-mL plastic syringe containing 4-mL 7% hydroxy ethyl starch and 6-mL acid citrate dextrose. The cells were allowed to gravity sediment at room temperature for 30 to 60 minutes until the plasma was clear of erythrocytes. The supernatant (leukocyte-rich plasma) was removed and centrifuged at 150 g for 8 minutes to obtain a leukocyte button. The supernatant (platelet-rich plasma) was removed and centrifuged at 450 g for 15 minutes to obtain platelet poor plasma. The resulting leukocyte button was incubated with 30 mCi of $^{99m}$Tc-HMPAO for 15 minutes with gentle and frequent swirling of the tube. Five milliliters of platelet poor plasma was added to the radiolabeled leukocyte suspension, which then was centrifuged at 150 g for 8 minutes. After the supernatant was removed, the resulting radiolabeled leukocyte button was resuspended with 5-mL platelet poor plasma. Then, 10-mCi $^{99m}$Tc-HMPAO-labeled leukocytes immediately were reinjected intravenously (the dose was scaled downward proportionately by weight for children). The patients were instructed to void before imaging. The abdomen and pelvis were imaged under a gamma camera equipped with a high-resolution, low-energy collimator starting at 30 to 60 minutes postinjection. An anterior image of the pelvis was acquired for 750,000 counts, and the acquisition time was recorded. Additional oblique or posterior images were acquired for the same time. This

Address reprint requests to Samuel L. Kipper, M.D., 4002 Vista Way, Department of Nuclear Medicine, Oceanside, CA 92056.
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imaging sequence was repeated at approximately 60-minute intervals until either the scan showed abnormal uptake, indicating a positive scan, or remained negative through 3 hours, at which time scanning was terminated. In all cases, scanning was completed and the results immediately reported to the surgeon before laparotomy or the decision not to operate occurred.

The Tc-WBC images were interpreted by one of two nuclear medicine physicians (SLK or DGE). The scan was positive if there was intra-abdominal localization of labeled leukocytes aside from the physiologic distribution of isotope in the liver, spleen, kidneys, bladder, bone marrow, and major blood vessels. Physiologic excretion of untagged isotope in the bile and urine precludes using Tc-WBC imaging for diagnosing inflammatory disease of the liver, bladder, kidneys, and gallbladder. A scan was negative if there was absence of abnormal intra-abdominal localization of Tc-WBCs through 3 hours of imaging after injection (Fig. 1A). Any scan that showed localized uptake in the right lower quadrant, right midabdomen, or midpelvis or that showed diffuse lower abdominal uptake (possible perforation) was interpreted as positive for acute appendicitis. An example of a typical positive scan is shown in Figure 1B. Abnormal uptake in organs outside of the right lower quadrant and pelvis (*i.e.*, colon, small bowel, or pancreas) was considered positive for inflammatory disease but not for acute appendicitis.

All patients were followed clinically for a minimum of 1 month after the Tc-WBC scan. In positive cases in which surgical operation was performed, the diagnostic accuracy was established by the microscopic pathologic diagnosis. In nonsurgical cases of intra-abdominal inflammatory or ischemic disease, the diagnosis was established by interviewing the attending physician, by chart review, and by subsequent patient outcome. Failure to detect an inflammatory cause of abdominal pain, negative exploratory laparotomy, absence of abdominal symptoms 1 month after the scan, and/or identification of another cause of abdominal pain was used to rule out intra-abdominal inflammatory and ischemic disease in the patients with negative Tc-WBC scans.

We studied the time to diagnosis after injection of Tc-WBCs for positive scans and determined sensitivity, specificity, accuracy, and positive and negative predictive values specifically for appendicitis as well as for other inflammatory and ischemic diseases. Several parameters of patient management were examined with respect to trends over the course of the study. We arbitrarily divided the patient population into four equal quartiles and monitored source of referral (outpatient *vs.* inpatient), disposition after negative scan, use of other imaging studies before and after Tc-WBC scan, and length of stay for hospitalized patients with negative scans. Differences between the groups were determined by Kruskal–Wallis test for nonparametric data.

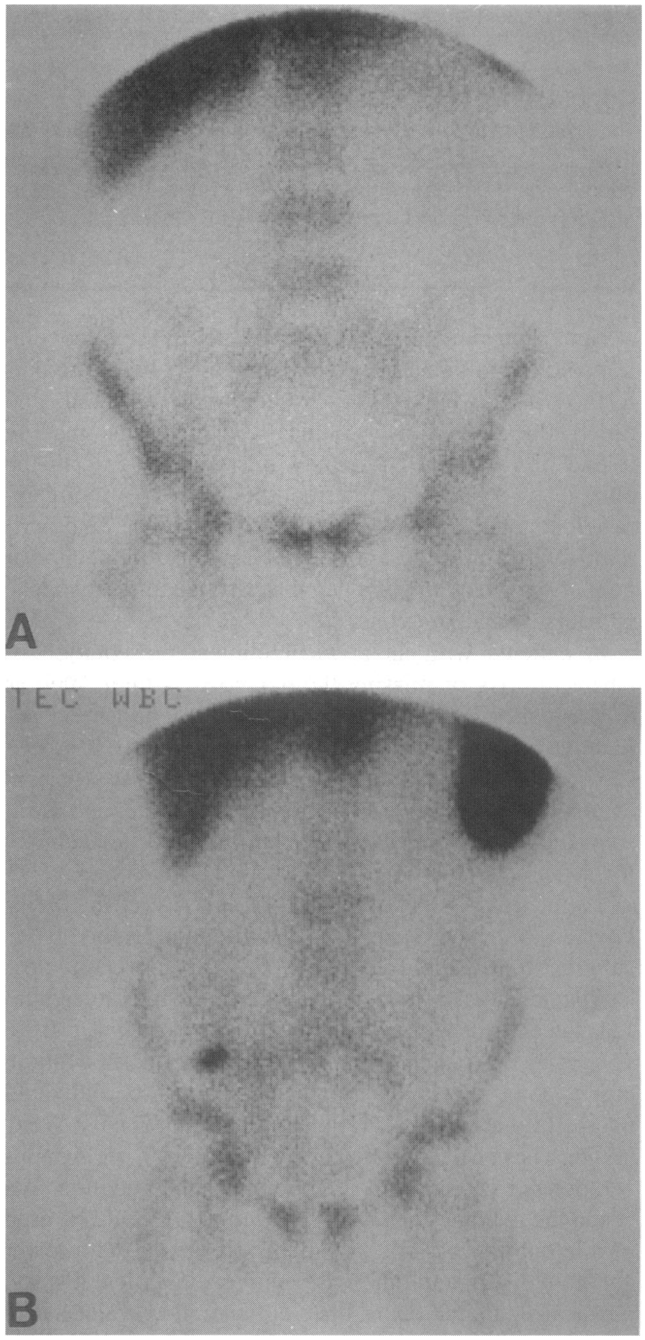


**Figure 1.** Negative and positive technetium-leukocyte (Tc-WBC) scans (A and B). These images are typical for negative and positive Tc-WBC scans. Note the presence of activity in the liver, spleen, aorta, and bone marrow in the normal scan. The positive scan shows abnormal activity in the right lower quadrant at 1 hour, and the patient had unperforated appendicitis at operation.

Table 1. POSITIVE SCANS

| Disease | Number | Scan Findings | Number Operated (number indicated) | Read Positive for Appendicitis | Read Positive for Other |
|---|---|---|---|---|---|
| Acute appendicitis | 37 | Focal RLQ or diffuse uptake with RLQ activity | 37(37) | 37 | 0 |
| Perforated appendix | 13 | Focal RLQ or diffuse uptake with RLQ activity | 13(13) | 13 | 0 |
| Sigmoid Diverticulitis | 3 | LLQ | 3(3) | 1 | 2 |
| Crohn's disease | 1 | Colon only | 0(0) | 0 | 1 |
| Cecal ulcer | 1 | RLQ | 1(1) | 1 | 0 |
| Cecal diverticulitis | 1 | RLQ diffuse | 1(1) | 1 | 0 |
| Cecal infarction | 1 | RLQ | 1(1) | 1 | 0 |
| Left tubo-ovarian abscess | 1 | LLQ | 1(1) | 0 | 1 |
| Endometritis | 2 | Uterus | 0(0) | 0 | 2 |
| Salpingitis | 2 | RLQ | 1(0) | 2 | 0 |
| Pancreatitis | 2 | RLQ with spread outside RLQ Upper abdominal diffuse | 0(0) | 2 | 0 |
| Perforated duodenal ulcer | 1 | RUQ | 1(1) | 0 | 1 |
| Abdominal pain only | 3 | RLQ | 1(0) | 3 | 0 |
| Total | 68 | | 60(58) | 61 | 7 |

RLQ = right lower quadrant; LLQ = left lower quadrant; RUQ = right upper quadrant.

## RESULTS

During the study period, 124 patients were referred to the Nuclear Medicine Department for Tc-WBC imaging to rule out appendicitis. All patients referred completed the imaging protocol, and there was 100% clinical follow-up. The first quartile of patients (n = 31) was acquired over the period from November 1991 through May 1994. The second quartile was from June 1994 to February 1995, the third quartile was from March 1995 through August 1995, and the fourth quartile was from September 1995 through December 1995. Of the 124 patients entered, 63 were male and 61 were female. There were 18 children younger than 13 years of age, 5 pregnant females, and 13 patients 60 years or older. The average age of the patients in the study was 30.6 years, ranging from 3 to 88 years. There was a nearly even split between positive and negative studies in the atypical cases referred to the Nuclear Medicine Department. No patient was operated on before the results of the scan were made known to the attending surgeon.

Table 1 compares the final diagnosis, scan results, and surgical outcome in 68 patients with positive scans for intra-abdominal inflammatory disease. Sixty-one scans were positive for appendicitis and 7 were positive for intra-abdominal inflammatory disease other than appendicitis. Fifty of the 61 scans read as positive for appendicitis correctly identified acute appendicitis as the source of abdominal pain. Sixty-five of 68 positive scans correctly identified an inflammatory source of abdominal pain. Of the 11 patients with false-positive scans for appendicitis, 4 required surgery (1 each for cecal diverticulitis, cecal infarction, cecal ulcer, and perforated sigmoid diverticulitis). The other seven had nonsurgical disease, including salpingitis in two, pancreatitis in two, and abdominal pain of unknown cause in three. Only two patients with false-positive scans underwent surgery that was not indicated. Acute right-sided salpingitis was found in one patient, and no evidence of inflammation was found in the other patient. The seven patients with positive scans for inflammatory disease other than appendicitis proved to have sigmoid diverticulitis in two, endometritis in two, Crohn's colitis, left tubo-ovarian abscess, and perforated duodenal ulcer in one each. Of these seven, four required surgical intervention.

Table 2 compares the scan findings with their ability to detect and exclude acute appendicitis and other intra-abdominal inflammatory disease. Diffuse lower abdominal uptake was somewhat predictive for appendiceal perforation. Appendiceal perforation was found in 8 of 13 patients showing this scan finding. Pancreatitis, nonperforated appendicitis, perforated sigmoid diverticulitis, and salpingitis also presented similar scan findings. Of the 13 patients with appendiceal perforation, 8 had diffuse lower abdominal uptake and 5 had focal right lower quadrant

Table 2. $^{99m}$Tc-HMPAO WHITE BLOOD CELL SCAN RESULTS VERSUS FINAL DIAGNOSIS*

| Scan Pattern | Acute Appendicitis | Perforated Appendix | Inflammatory Diseases (other) | Negative |
|---|---|---|---|---|
| Focal RLQ | 36 | 5 | 4 | 3 |
| Diffuse RLQ | 1 | 8 | 4 | 0 |
| Positive other | 0 | 0 | 7 | 0 |
| Negative | 1 | 0 | 0 | 55 |

RLQ = right lower quadrant.
* For inflammatory diseases: sensitivity = 98%; specificity = 95%; accuracy = 97%; positive predictive value = 96%; negative predictive value = 98%. For appendicitis: sensitivity = 98%; specificity = 85%; accuracy = 90%; positive predictive value = 82%; negative predictive value = 98%.

uptake. Overall, Tc-WBC imaging correctly diagnosed appendicitis in 50 of 51 cases for a sensitivity of 98% and correctly excluded appendicitis in 62 of 73 cases for a specificity of 85%. The accuracy, positive, and negative predictive values for acute appendicitis were 90%, 82%, and 98%, respectively. The Tc-WBC imaging correctly identified an inflammatory source of abdominal pain in 65 of 66 patients proved to have intra-abdominal inflammation for a sensitivity of 98% and was correctly negative in 55 of 58 patients for a specificity of 95%. The accuracy, positive, and negative predictive values for intra-abdominal inflammatory disease were 97%, 96%, and 98%, respectively. In the subgroup of five pregnant patients, there were three true-positive scans for acute appendicitis and two true-negative scans.

Table 3 breaks out the management and outcome of the 56 patients with negative scans. Of these, 31 were allowed to return home and 21 were observed in the hospital and were subsequently determined to not have an acute abdomen. Three patients with negative scans underwent exploratory laparotomy because the surgeon did not believe the scan. Of these, two had normal appendices (true-negative scans) and one had appendicitis (false-negative scan). This latter patient presented early in the course of the study and had persistent tracer in the blood pool that masked the appendix at 3 hours. An oblique image was omitted inadvertently. After surgery, the surgeon brought the specimen to the Nuclear Medicine Department, where it was placed under the gamma camera and was found to be positive. After this false-negative scan, an oblique view was obtained in all patients with a negative scan at 3 hours and persistent activity in the blood pool. One other patient with a negative study result underwent further work-up, the results of which showed acute cholecystitis, and he subsequently underwent cholecystectomy.

Labeling the tracer takes 2 hours. However, once the labeled leukocytes are injected, more than half of the scans are clearly positive at 1 hour and almost three fourths by 2 hours. Patients with negative scans all required 3 hours scan time before being declared negative.

The number of additional adjunctive radiographic studies performed (except plain abdominal x-ray) decreased substantially. During the course of the study, there was decreasing use of ultrasound, CT scan, and BE by the clinicians managing the patients. Most of the decline in adjunctive testing came in the use of ultrasound, which, in our experience, has not been a reliable test.

We also noted a change in the referral source from primarily inpatient to primarily outpatient sources. Outpatient referrals, primarily from the emergency department, for the first quartile of patients accounted for only 38% and increased to 87% by the last quartile. We also noted a decreasing tendency for inpatient observation of patients with negative scans from 73% to 13% over the course of the study. Similarly, the average length of stay for patients with negative scans also had decreased significantly from an average of 3.2 days to <1 day, $p < 0.02$.

Table 3. NEGATIVE SCANS

| Negative Scan Management | Number |
|---|---|
| Sent home with follow-up | 31 |
| Admitted with rule out appendicitis as diagnosis | 21 |
| Surgery (total) | 4 |
| Normal appendix | 2 |
| Cholecystitis | 1 |
| Appendicitis (false negative) | 1 |

## DISCUSSION

The accuracy of clinical judgment in diagnosing acute appendicitis generally has not changed much over the past 50 years, and negative laparotomy rates of 15% and 30% still are considered acceptable.[2] In the early stages of the disease, the symptoms can be minimal and patients do not appear to be particularly ill. The classical presentation of appendicitis is said to be present in less than half of those presenting to the hospital who subsequently are found to have the disease.[7] This is particularly true of children, the elderly, and female patients in whom other lower abdominal conditions are commonplace.[8-10] In pregnant women, appendicitis is the most common non-obstetric surgical disease and because the appendix is displaced, the presentation is atypical and diagnosis may be difficult. Delay in operation in this group runs a higher risk of complications as well as maternal and fetal death.[11] It is therefore incumbent on surgeons managing patients with abdominal pain to correctly and quickly diagnose and treat patients appropriately.

In patients with abdominal pain and atypical or equivocal signs, symptoms, or laboratory tests, adjunctive imaging studies often are used to increase early diagnostic accuracy. These include flat and upright abdominal x-ray, graded compression ultrasound, BE, or CT scan. Plain films of the abdomen occasionally will show a calcified fecalith, free peritoneal gas, or abnormal right lower quadrant gas patterns, but these findings are infrequent or nonspecific.

Other than routine abdominal x-rays, ultrasound probably is the most commonly used adjunctive test for the patient with an atypical presentation. The diagnosis is suggested by a dilated appendiceal lumen and a thick wall. However, it has an accuracy of only 30% in patients with early appendicitis because the appendix may not display the changes required for visualization. In addition, a skilled technician is required to perform the examination.[12-15] With sensitivity ranging from 75% to 89% at best, a negative ultrasound examination result does not adequately rule out acute appendicitis and inpatient observation usually is required.

The BEs are difficult to perform emergently, fraught with frequent technical problems, and, as with ultrasound, failure to visualize the appendix does not rule out appendicitis.[16] High-resolution CT with intravenous and oral contrast has a reported sensitivity of 96% in one study in which it was compared to ultrasound for the diagnosis of acute appendicitis.[17] However, CT scan is too expensive for widespread use as a screening tool, and it may not be sensitive for early appendicitis before anatomic changes are evident. A recent study by Sarfati et al.[4] found that neither preoperative ultrasound, CT scan, nor BE reduced the number of negative laparotomies or perforation rate. They concluded that although useful in individual cases, these adjunctive tests did not affect overall patient outcome.

Laparoscopy has been used to diagnose acute appendicitis in difficult cases. Its advantage is that if acute appendicitis is found, then therapy can proceed immediately. However, its disadvantages are many, including requirement for admission to the hospital, general anesthesia, the expense of surgery, difficulty in patients with prior abdominal operations, inability to visualize the appendix in 15% of cases, and higher morbidity than imaging tests.[18-20] For these reasons, it is unlikely to be used as a screening test.

Radionuclide imaging using radiolabeled leukocytes holds the possibility of being able to diagnose early appendicitis at a stage when the inflammatory process is beginning, and preliminary studies have shown some promise. The approach taken by Henneman et al.[21,22] involved labeling of WBCs with $^{99m}$Tc-colloid albumin particles. A high negative predictive value was found by these authors, particularly in children, but the positive predictive value in adult women was quite low. They also reported indeterminate results in 17% of cases. There have been only a few studies using $^{99m}$Tc-HMPAO-labeled WBC imaging for acute appendicitis. Foley et al.,[23] in their initial series of 30 patients, found that the specificity was 100% but the sensitivity was only 81%, a false-negative rate of 3 (16%) of 19 patients. In a subsequent study adding 37 more patients, they improved sensitivity to 85% but specificity declined to 93%, and the overall accuracy was 89%.[24]

Our findings are different from those of Foley et al.[23] and are considerably better with respect to sensitivity (*i.e.*, fewer false-negatives) and we attribute this to differences in technique. We use a higher but acceptable dose of $^{99m}$Tc (10 mCi *vs.* 5 mCi), labeled a greater number of leukocytes by drawing a larger volume of blood (50 mL *vs.* 25 mL), imaged with higher frequency after injection, and performed oblique and posterior views when necessary for retrocolic appendicitis and avoided overlapping the appendix and the iliac vessels. The lone false-negative scan occurred early in the study and, when reviewed retrospectively, probably would have been avoided if oblique imaging had been done.

In the patient with right lower quadrant pain and an equivocal examination, admission to the hospital for observation still is considered standard of care. This increases the cost of medical care in addition to increasing the risk of perforation by delaying operation. The morbidity accompanying perforation includes peritonitis and intra-abdominal abscess and is directly responsible for increasing hospital stay, cost of care, and financial loss from missed work.[25] The results of our study suggest that Tc-WBC imaging may be used to limit the number of ancillary imaging studies and avoid hospital admission for observation in addition to reducing the false-negative laparotomy rate. Specifically, the high negative predictive value of this imaging test suggests that in patients with a negative scan, outpatient management may be possible. If so, it may be possible to use Tc-WBC imaging as a screening test in patients with an atypical presentation of acute appendicitis.

The management of patients with positive scans requires clinical input from a surgeon. Most of the positive scans were caused by either appendicitis or another inflammatory condition requiring surgery. A variety of right lower quadrant intra-abdominal inflammatory processes may be detected with Tc-WBC imaging, including diverticulitis, inflammatory bowel disease, salpingitis, cecal ulcer, abscess, and even bowel ischemia. The Tc-WBC scan may not always be able to differentiate appendicitis from some of these other entities, hence the specificity for appendicitis of 85%. Therefore, positive scans must always be interpreted in light of the overall clinical picture. Fortunately, only two patients with a preoperative diagnosis of acute appendicitis underwent unnecessary exploratory laparotomy because of right lower quadrant uptake that was not caused by appendicitis. One patient was found to have right-sided salpingitis, and the other was found to have no evidence of inflammatory disease at surgery. The information obtained from a positive scan was almost always useful in determining whether an inflammatory condition was responsible for abdominal pain and, together with the history and physical examination results, suggested the best way to proceed with management.

The surgeons and emergency department physicians initially were slow to use this new test, but as familiarity grew, the frequency of patient referrals increased. The first 31 scans were requested over a 2 ½-year period. Since then, this number is requested approximately every 2 to 3 months. Does this represent excessive use of this test? There were 199 appendectomies performed for acute appendicitis during 1995 at our institution. During this same period, there were 34 appendectomies performed in our study group representing 17% of total appendectomies. Therefore, most patients with acute appendicitis at our institution do not require a Tc-WBC scan or any other ancillary imaging study to aid in the diagnosis, because they probably were considered typical cases. Based on the published literature, we would have expected that the negative laparotomy rate in a group of patients with an equivocal presentation for acute appendicitis would be at least 20% to 30%. The negative laparotomy rate in our group of equivocal patients was to 3.9% (2 in 51), an order of magnitude lower than expected.

By immediately reporting the scan results to the referring physician, we were able to document their effect on patient management and outcome as the study progressed. We showed a significant change in management of patients with an equivocal presentation of acute appendicitis. We documented definite trends toward obtaining the scan in the outpatient setting rather than after admission, ordering of fewer adjunctive tests, and earlier discharge from the hospital if the scan was negative. These trends suggest that the Tc-WBC scan has evolved into a valuable diagnostic tool that is directing the management of patients with an equivocal presentation of acute appendicitis. Although we have not calculated the actual cost savings involved, we believe that by limiting unnecessary hospital admission for observation, decreasing the length of hospital stay in patients already admitted for abdominal pain and subsequently not found to have appendicitis, reducing the use of other diagnostic tests, and lowering the negative laparotomy rate, we have shown that Tc-WBC imaging as a screening test in the patient with an atypical or equivocal presentation of acute appendicitis is likely cost effective and favorably impacts clinical outcome.

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