**INVITED COMMENTARY**

# Imaging Acute Appendicitis: An Opportunity for Nuclear Medicine in the Surgical Emergency Room

Acute diagnostic procedures in nuclear medicine have proven to directly affect the treatment of patients suspected of having pulmonary embolism and acute cardiac conditions. However, most routinely available nuclear medicine techniques fail to contribute to the diagnostic work-up of patients who are suspected of having an acute abdominal infection requiring immediate surgical attention. A scintigraphic technique can play a role in this clinical situation only when 2 important requirements are met. The first is diagnostic accuracy. Poor accuracy is an important limitation of most of these procedures. Negative or positive predictive values have to be high to warrant a change from immediate surgery to observation or even discharge, and vice versa. When the positive predictive value of a procedure is high, positive findings are convincing enough to warrant surgery, even in patients lacking some typical signs and symptoms. Conversely, when the negative predictive value is high, the procedure can result in adoption of a conservative regimen. Obviously, the ideal situation would be for both parameters to be such that any outcome of the procedure would be decisive.

The second important requirement is the interval between referral and final reading of the scintigraphic images. This factor plays an important role in patients who may have an acute focal infection for which surgery is indicated. For example, $^{99m}$Tc-labeled white blood cell imaging has the required level of performance for acute abdominal infections (*1*), but the preparation time may prevent incorporation of the procedure into a diagnostic work-up during office hours. Moreover, many nuclear medicine departments do not have an on-site cell-labeling facility.

In this issue of *The Journal of Nuclear Medicine*, Kipper et al. (*2*) describe the use of an anti-CD15 immunoglobulin M (IgM) antibody that has attractive characteristics and meets the 2 important requirements. The antibody binds with high affinity to an epitope on granulocyte membranes. The procedure provides positive images of the infectious focus early after injection. Target-to-background ratios are favorably influenced by rapid clearance of the IgM antibody from the blood pool to the liver and spleen. Finally, the antibody can be conveniently labeled with $^{99m}$Tc in a simple and fast procedure.

Given these theoretically attractive characteristics of the anti-CD15 IgM antibody, the question is how well the agent performs in clinical studies. By studying patients with atypical appendicitis, Kipper et al. (*2*) chose a relatively difficult category. The turnover time seems acceptable, with a 2-h average interval between study request and final image interpretation. Because all 26 cases of appendicitis were correctly depicted, the negative predictive value in this series was 100%, ameliorating the concern about missing a case of acute appendicitis. Because only an additional 3 patients were taken to surgery without subsequent proof of appendicitis, the rate of laparotomies with negative findings was, at 10%, remarkably low. As the authors state, a negative-finding rate as high as 40% would not be unusual in this category of patient. The study appears to show a significantly decreased false-negative rate in comparison with a setting in which anti-CD15 imaging is not available. Assuming an $\alpha$ level of 0.05 (type I error, or the chance that incorrect interpretation of imaging results will reduce the number of laparotomies with negative findings) and a power of 0.80 (type II error, or the chance that incorrect interpretation of imaging results will not reduce the number of laparotomies with negative findings), the study significantly reduces the number of false-negative laparotomies if the percentage of false-negative laparotomies is higher than 25% when anti-CD15 IgM imaging is not available.

The pitfalls of the study of Kipper et al. (*2*) fall into 2 categories: the study design and the antibody itself. An important limitation is the surgeon's knowing the results of anti-CD15 scintigraphy. As a result, the true impact of the procedure on patient management is difficult to estimate. Therefore, enthusiasm about the current results and a rush toward introduction into clinical practice should be tempered. A larger, randomized, multicenter trial in which the surgeon is unaware of the results of the experimental procedure and the nuclear medicine physician is unaware of the clinical data is warranted. Furthermore, a clear definition of equivocal appendicitis is mandatory in such a study: in the study of Kipper et al. (*2*), 4 criteria are mentioned without further explanation. However, if a trial such as we describe confirms the results of Kipper et al., this nuclear medicine procedure could have a remarkable impact on the

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number of laparotomies and, thus, on the need for hospitalization.

The radiopharmaceutical itself needs careful evaluation. In the study of Kipper et al. (*2*), no white blood cell counts were obtained directly after infusion of the radiopharmaceutical. However, the antibody has been reported to cause an almost immediate—albeit transient—drop in peripheral leukocyte counts (*3*). Similar observations have been made after the administration of chemotactic peptides and interleukin-8 in experimental models of infection (*4,5*). Although the leukocyte counts spontaneously recover within 1 h after anti-CD15 IgM administration without medical intervention, and chemotactic ability and directional migration seem unaffected (*3,6*), careful attention must be paid to this phenomenon because leucocytopenia—even transient—caused by a diagnostic test is undesirable in patients with acute infection. Nevertheless, the anti-CD15 antibody preparation appears to be clinically safe. Additionally, Kipper et al. report that labeling conditions influence the renal excretion of the radiolabel, raising questions on in vivo stability of the radiopharmaceutical and indicating that the radiopharmaceutical is poorly defined chemically. Perhaps further optimization of the $^{99m}$Tc-labeling technology could improve in vivo stability of the radiopharmaceutical.

Incorporation of such a scintigraphic procedure into clinical protocols for diagnosis of equivocal acute appendicitis will significant affect the management of nuclear medicine departments. A 24-h service must be in place, and the labeling facilities must be available in house.

How can the $^{99m}$Tc-labeled anti-CD15 antibody be positioned in the array of agents available for scintigraphic imaging of infectious disease, focusing on patients suspected of having appendicitis? Currently, the agent of choice for imaging acute abdominal infection and inflammation is white blood cells labeled with $^{99m}$Tc-labeled hexamethylpropyleneamine oxime. Adequate results in cases of equivocal acute appendicitis can be achieved with this technique: in 73% of scans, pathologically increased uptake was observed within 2 h after injection, providing a negative predictive value of 98% and a negative laparotomy rate of less than 4% (*1*). However, the need for cell-labeling facilities, experienced staff, and the 2- to 3-h preparation time hamper widespread use for this indication. Additionally, the need to handle blood is an unattractive but unavoidable feature of the technique. Labeled polyclonal immunoglobulin or labeled antigranulocyte monoclonal antibody fragments are prepared similarly to $^{99m}$Tc-labeled anti-CD15 antibody, but all have drawbacks caused by low negative predictive values (less than 90%) and longer or more demanding imaging procedures (e.g., SPECT) (*7–9*). These drawbacks relate to relatively low uptake in the focus or persistently high blood pool and background activity. Whether surgeons will accept such high false-negative rates is highly questionable. Moreover, sick patients with abdominal pain much better tolerate fast planar imaging than SPECT. Compared with the study of Kipper et al. (*2*), none of the alternative agents matched the performance of $^{99m}$Tc-labeled anti-CD15 imaging in this category of patients. However, other labeled proteins may find their way into clinical practice for other indications, because relatively high uptake of $^{99m}$Tc-labeled anti-CD15 in the liver and spleen make unlikely the equal or greater success of this agent in the upper abdomen.

Other, nonscintigraphic techniques are also being developed to improve the diagnostic work-up of patients with acute appendicitis, especially children and female patients of reproductive age. A study has shown that sonography does not significantly affect the surgeon's clinical confidence in the diagnosis (*10*). In contrast, CT with rectal contrast material and helical CT have been shown to have a significant effect (*10,11*). Laparoscopy has become a standard procedure in recent years and can be useful in cases of atypical appendicitis. Laparoscopy, by directly revealing other causes of abdominal pain, reduces the frequency of appendectomy (*12–14*). However, laparoscopy is invasive, and its impact on the final outcome (e.g., length of hospital stay, return to normal daily activity, need for antibiotic treatment) is controversial, as recently described in a review by Fingerhut et al. (*15*).

In conclusion, nuclear medicine will be on its way into the surgical emergency room when 3 conditions are met: when $^{99m}$Tc-labeled anti-CD15 antibody imaging for equivocal appendicitis has been confirmed in larger, randomized trials; when no safety issues prevent use of the antibody; and when nuclear medicine departments can provide 24-h service.

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## REFERENCES

1. Rypins EB, Evans DG, Hinrichs W, Kipper SL. Tc-99m-HMPAO white blood cell scan for diagnosis of acute appendicitis in patients with equivocal clinical presentation. *Ann Surg.* 1997;226: 58–65.
2. Kipper SL, Rypins EB, Evans DG, Thakur ML, Smith TD, Rhodes B. Neutrophil-specific $^{99m}$Tc-labeled anti-CD15 monoclonal antibody imaging for diagnosis of equivocal appendicitis. *J Nucl Med.* 2000;41:449–455.
3. Gratz S, Behr T, Herrman A, Dresing K, et al. Intraindividual comparison of Tc-99m-labelled anti-SSEA-1 antigranulocyte antibody and Tc-99m-HMPAO labelled white blood cells for the imaging of infection. *Eur J Nucl Med.* 1998;25;386–393.
4. Babich JW, Graham W, Barrow SA, et al. Technetium-99m-labeled chemotactic peptides: comparison with indium-111-labeled white blood cells for localizing acute bacterial infection in the rabbit. *J Nucl Med.* 1993;34:2176–2181.
5. van der Laken CJ, Boerman OC, Oyen WJG, van de Ven MTP, van der Meer JWM, Corstens FHM. Radiolabeled interleukin-8: specific scintigraphic detection of infection within a few hours. *J Nucl Med.* 2000;41:463–469.
6. Thakur ML, Lee J, DeFulvio JD, Richard MD, Park CH. Human neutrophils: evaluation of adherence, chemotaxis and phagocytosis, following interaction with radiolabelled antibodies. *Nucl Med Commun.* 1990;11:37–43.
7. Barron B, Hanna C, Passalaqua AM, Lamki L, Wegener WA, Goldenberg DM, for the LeukoScan Appendicitis Clinical Trial Group. Rapid diagnostic imaging of acute, nonclassic appendicitis by leukoscintigraphy with sulesomab, a technetium 99m-

labeled antigranulocyte antibody Fab' fragment. *Surgery.* 1999;125:288–296.
8. Biersack HJ, Overbeck B, Ott G, et al. Tc-99m labeled monoclonal antibodies against granulocytes (BW 250/183) in the detection of appendicitis. *Clin Nucl Med.* 1993;18:371–376.
9. Wong DW, Vasinrapee P, Spieth ME, Cook RE, Ansari AN, Jones M Jr, Mandal A. Rapid detection of acute appendicitis with Tc-99m-labeled intact polyvalent human immune globulin. *J Am Coll Surg.* 1997;185:534–543.
10. Garcia Pena BM, Mandl KD, Kraus SJ, et al. Ultrasonography and limited computed tomography in the diagnosis and management of appendicitis in children. *JAMA.* 1999;15:1041–1046.
11. Rao PM, Rhea JT, Novelline RA. Helical CT of appendicitis and diverticulitis. *Radiol Clin North Am.* 1999;37:895–910.
12. Barrat C, Catheline JM, Rizk N, Champault GG. Does laparoscopy reduce the incidence of unnecessary appendicectomies? *Surg Laparosc Endosc.* 1999;9:27–31.
13. Thorell A, Grondal S, Schedvins K, Wallin G. Value of diagnostic laparoscopy in fertile women with suspected appendicitis. *Eur J Surg.* 1999;165:751–754.
14. Tytgat SH, Bakker XR, Butzelaar RM. Laparoscopic evaluation of patients with suspected acute appendicitis. *Surg Endosc.* 1998;12:918–920.
15. Fingerhut A, Millat B, Borrie F. Laparoscopic versus open appendectomy: time to decide. *World J Surg.* 1999;23:835–845.