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Seminars in
NUCLEAR
MEDICINE

# Pitfalls and Limitations of Radionuclide and Hybrid Imaging in Infection and Inflammation

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**Both the referring clinician and the nuclear medicine specialist must be aware of the main known or potential pitfalls that can occur in infection and inflammation imaging. They must decide in consensus which tracer and which imaging protocol should be used for a specific indication. This article provides an overview of all the pitfalls and limitations of nuclear medicine techniques to image infections and inflammation. Both general pitfalls and pitfalls in specific clinical entities are discussed.**
**Semin Nucl Med 45:500-512** 

## Introduction

In recent years, our understanding and knowledge of the pathophysiology and characteristics of infectious and inflammatory diseases has dramatically improved. New hybrid imaging systems and new radiopharmaceuticals have been developed, and new guidelines implemented. The total number of nuclear medicine procedures for these indications is increasing. Alternatively said and not to be ignored, nuclear imaging of infections and inflammation is booming.

Looking back at the article describing pitfalls in 1996 (which was 19 years ago), no attention was paid at all to infection and inflammation. It is now time to change that. Both the referring clinician and the reporting nuclear medicine physician should be aware of existing pitfalls in various indications. This will enable to recognize and reduce the number of false-negative and false-positive findings, leading to a higher diagnostic accuracy by shared knowledge, which will allow us to implement guidelines regarding the use of specific tracers at particular time points during the course of disease.

The primary goal of this article is to increase the knowledge of the reader for the recognition of pitfalls in infectious and inflammatory diseases. We will not focus on pitfalls that are caused by the use of different camera systems, for example, pitfalls due to differences in spatial resolution (PET only vs PET/CT, SPECT vs PET, etc.) and partial volume effects that are presented in another article of this special issue. We first focus on general pitfalls that may cause problems regarding the acquisition and interpretation of the scans performed in cases with suspected or known infectious and inflammatory processes. Additionally, we highlight the most important pitfalls that can occur in specific clinical entities.

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## General Pitfalls

### The Imaging Request

Clinicians often struggle with questions in patients dealing with presumed or established infectious or inflammatory disorders. Their main questions are as follows: Is there an infectious focus or a sign of inflammation? Is it an acute or chronic process? Is it a high- or low-grade infection? What is the size and extent of the process? Is this the only site of disease or did infectious metastases spread? Should treatment be stopped, changed, or continued?

These questions are not easy to answer beyond any doubt. There is no "gold standard" tracer or imaging modality that can provide all the answers accurately. It is therefore important to define the expected outcome of the requested study to be able to perform the proper acquisition protocol with the best available tracer. For example, if from a clinical point of view it is important to distinguish infection from sterile inflammation, then $^{18}$F-FDG might not be the best option, as uptake can be seen in both processes. In this case, labeled white blood cells

 http://dx.doi.org/10.1053/j.semnuclmed.2015.02.005
0001-2998/

(WBC) should be the tracer of choice. On the contrary, when a clinician is looking for the precise localizations of an already known infectious or inflammatory process, FDG is the tracer of choice. Another example is the acquisition protocol for WBC scintigraphy, which depends on the indication. For a suspected vascular graft in the abdomen, acquisition times should be at 1 and 3-4 hours after reinjection, whereas for a suspected infection of a hip or knee prosthesis, acquisition times should be 3-4 and 20-24 hours after injection. A final example is the optimal time point to evaluate therapy—should it be 6 weeks, 3 months, or 6 months? Should the therapy then be withdrawn completely or should the scan be acquired during therapy? This depends on a combination of factors including also the specific indication and the type of therapy. All these questions have to be carefully weighted before requesting a functional or metabolic imaging test (by the clinician) and before approving it (by the nuclear medicine specialist).

## WBC Scintigraphy: Pitfalls in Labeling, Acquisition, and Interpretation

Most of the major problems with labeled WBC imaging arise from either the cell labeling procedure or from misreading the scans because of incorrect acquisition protocols or interpretation criteria or both.

WBCs should be labeled (either with $^{99m}$Tc-HMPAO or $^{111}$In-oxine) according to the 2010 published guidelines of the Inflammation and Infection Task Group of the European Association of Nuclear Medicine (EANM), which, beside indications and practical aspects, also include quality control and safety procedures.[1,2] These guidelines are written in accordance with the current European Union regulations and International Atomic Energy Agency recommendations. Disregarding these guidelines can result in pitfalls such as the lack of uptake in an infectious process or the presence of false-positive uptake in noninfected sites, for example, in the lungs (Fig. 1).

The use of incorrect acquisition protocols or interpretation criteria will result in a decrease in sensitivity, specificity, and diagnostic accuracy and explains the variable performance indices for WBC scintigraphy reported in the literature.[3,4] A correct acquisition protocol should include at least dual-time-point imaging corrected for time decay. Images should be displayed in number of counts, using the same intensity scale for both images, thereby avoiding operator bias related to intensity scale variability.[5,6]

Knowledge of normal (blood and bone marrow) WBC biodistribution, of variants of WBC localization in different tissues and organs, as well as of changes in uptake over time under different conditions is essential.[3] In general, visual analysis of the time-decay–corrected images is sufficient and has a high diagnostic accuracy. A focus of increasing uptake over time is considered positive for infection, whereas decreasing or stable uptake over time is considered negative. When visual analysis is doubtful, semiquantitative analysis can be helpful.[5,6] SPECT/CT has an established role when precise localization of findings is essential, and there is a need for anatomical landmarks (eg, in soft tissue infections,[7] endocarditis,[8] infected cardiac devices or vascular prostheses, and diabetic foot [9]). Even with the use of SPECT/CT, in some cases localization is difficult, such as that of intense WBC uptake close to the bone that can result in false-positive diagnosis of osteomyelitis.[5]

## FDG-PET: Pitfalls in Uptake and Interpretation

The major limitation of FDG is the inability of the tracer to discriminate between malignancy, infection, and inflammation. Accumulation of leukocytes, macrophages, monocytes, lymphocytes, and giant cells constitutes the body's response to injury and infection. Upregulation of glucose transporters has been demonstrated in all these cell lines and contributes to the uptake of detectable amounts of FDG in infection and inflammation, as well as in regenerating and traumatic processes. The reader has to be fully aware of these limitations; for example, to avoid potential pitfalls in skeletal FDG uptake, a careful evaluation of the combined CT component is necessary to exclude factors such as recent fractures as a cause of increased FDG uptake.

It is still controversial whether hyperglycemia or diabetes mellitus affects the sensitivity of FDG-PET imaging. Guidelines for FDG-PET/CT in patients with cancer recommend that FDG should not be administered when blood glucose levels exceed 200 mg/dL [10] or even 120 mg/dL [11] if clinically possible. However, studies in this field show mixed results. Reduced FDG uptake at higher glucose serum levels has been observed only in patients with pancreatic and lung cancer.[12] A large study by Rabkin et al showed that high glucose levels but not diabetes mellitus at the time of the study in the assessment of malignancy reduced the sensitivity of FDG-PET/CT. However, no significant effect on the false-negative rate was found in 123 patients with infection and inflammatory processes with either diabetes mellitus or hyperglycemia.[13] Therefore, recent implemented guidelines for FDG imaging in infections and inflammation published by a joint force of the EANM and Society of Nuclear Medicine (SNM) state that "although efforts should be made to decrease blood glucose to the lowest possible level, if the study is indicated in those with unstable or poorly controlled diabetes, hyperglycemia should not represent an absolute contraindication for performing the study."[14]

Kidney dysfunction may also influence scan quality. The target-to-background ratio will decrease owing to a higher and longer uptake in cardiovascular structures (high blood pool activity). Therefore, serum creatinine level or glomerular filtration rate or both should be checked before performing the study. Kidney function is already routinely checked clinically or before CT imaging with contrast.

Invasive procedures often results in increased FDG uptake owing to a regeneration and healing process. This nonspecific uptake may be seen in the first 2 weeks after surgery or scars in the skin or soft tissue or both, but it may last for up to 6 months after surgery in bones.[15,16] A negative FDG study finding at the site of surgery is clear, but a positive scan result must be interpreted with caution as long-lasting nonspecific uptake may be seen for a long time.

In children and young adults, physiological FDG uptake in the thymus has been reported, mainly after chemotherapy.[17] Thymic hyperplasia and regrowth may occur in