

## Overview of nuclear imaging techniques for the detection of infection and inflammation

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Diagnosis and treatment of infection and inflammation have become increasingly important in the last decades. Factors responsible for this development are the ongoing ageing of the patient population and the increasing use of antibiotics, leading to insensitivity for some of these pharmaceuticals. Another important issue is the growing number of patients with organ transplants and increased application of chemotherapy regimes; in both situations the immune system becomes compromised (by anti-rejection medication in the former and by a direct effect on the bone marrow in the latter), a situation in which even very mild infections can cause serious and occasionally life-threatening illness. Since the early days of nuclear medicine, imaging techniques for the detection of infection and inflammation have evolved significantly. Nowadays, a wide array of various techniques and radiopharmaceuticals are available in this field. Each one has its own benefits and limitations, which are related to, for example, biodistribution and photon energy. It is the responsibility of the nuclear medicinist, often after backtalk with the referring specialist, to make the right choice of technique and perform the scan that answers the clinical question best.

When a focus of infection needs to be assessed or ruled out, it is important to realize that virtually all of the available techniques used in nuclear medicine visualise the process of inflammation rather than infection itself. At present inflammation is defined as the reaction of tissue to any injury, aiming at bringing serum molecules and cells of the immune system to the area where the injury takes place. Infection is defined as any injury caused by microorganisms. Radiolabeled compounds can be classified as non/ low specific or moderate specific, the former meaning that accumulation of the tracer at the focus of infection is exclusively or mainly caused by increased permeability of small vessels (a process necessary to enhance the efflux of white blood cells). Unfortunately, a compound that specifically accumulates at the site of microorganisms infiltration does not exist. Even infection imaging by using the radiolabeled antibiotic  $^{99m}\text{Tc}$ -ciprofloxacin (Infecton®), which theoretically homes to bacteria only, depends more or less on non-specific increased vascular permeability.

Examples of radiopharmaceuticals lacking specificity are  $^{67}\text{Ga}$ -citrate and human nonspecific polyclonal immunoglobulin (HIG).  $^{67}\text{Ga}$ -citrate has less favorable imaging characteristics such as a long physical half-life (78 h) and multiple high-energy gamma radiation (93–889 keV), causing high radiation absorbed doses. For these reasons it is less used in routine clinical practice, but still plays an important role in selected conditions, such as in patients with suspected vertebral osteomyelitis or with fever of unknown origin. Human nonspecific polyclonal immunoglobulin (HIG) can be labeled with  $^{111}\text{In}$  or with  $^{99m}\text{Tc}$ ; both compounds have different characteristics and applicability. An important indication is a (suspected) orthopaedic prosthesis infection.

Of those techniques that show more specific accumulation at the site of infection, radiolabeling of leukocytes is probably the most important. Leukocyte labeling can be performed *in vivo* (inside the patient's body) or *in vitro* (in the laboratory), which is the most used technique. With the *in vitro* labeling, 50 millilitres of blood are sampled from the patient and washed in a complex process. The leukocytes are separated from the rest of the blood cells, labeled with  $^{111}\text{In}$  or  $^{99m}\text{Tc}$  (depending on the indication), and finally re-injected. Examples of indications of leukocyte scintigraphy are osteomyelitis and soft tissue infections, but also inflammatory diseases such as colitis ulcerosa and Crohn's disease. Although highly sensitive, this technique is very laborious. A more important drawback is the fact that blood has to be handled outside the patient. Because of this, safety procedures allow handling of only one blood sample at a time to avoid cross-contamination with blood from other patients. Leukocyte labeling *in vivo*, which is not restricted by the aforementioned problems, can be performed after injection of an intact monoclonal whole mouse antibody (Granulosint®) or mouse antibody fragments (sulesomab; Leukoscan®). Unlike using *in vitro* labeled leukocytes, the administration of mouse antibodies can lead to sensitization of the human immune system. After repeated administration, the immunologic response can cause

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altered pharmacokinetics (and thereby lowering sensitivity) or, even worse, serious allergic reactions. When a mouse antibody fragment is used, this risk is negligible. There are many different indications for the use of *in vivo* labeled leukocytes.

Another choice of a scintigraphic technique with more specific radiotracer accumulation is the use of radiolabeled cytokines. Cytokines are (glyco)proteins and peptides that make it possible for cells to communicate with each other, thereby regulating the transportation of inflammatory cells towards the focus of infection. Examples are  $^{99m}\text{Tc}$  labeled interleukine-8, used in patients with infected joint prosthesis and osteomyelitis, and  $^{123}\text{I}$  labeled interleukine-2, which is able to visualize the auto-immune process against the insulin-producing cells of the pancreas in patients with diabetes mellitus. At the moment, radiolabeled cytokines are still almost exclusively used in research settings. However, future routine clinical applications are likely.

As the worldwide availability of PET (and PET/CT) scanners further increases, it is to be expected that imaging of infection and inflammation with  $^{18}\text{F}$ -FDG will take an important place in the routine clinical practice of nuclear medicine. Although oncologic staging is probably the most applied indication of  $^{18}\text{F}$ -FDG PET (using the principle that malignant cells with high metabolic needs show pathologically increased uptake of  $^{18}\text{F}$ -FDG), activated leukocytes also exhibit enhanced uptake, making it possible to visualize inflammatory and infectious processes. Some advantages compared to other nuclear techniques are the short incubation time (1 hour), high-resolution tomographic imaging and the possibility to perform semi-quantitative uptake measurement using a standardized uptake value (SUV). However, proper preparation of the patient is required to assure the highest possible sensitivity and specificity. When carefully applied,  $^{18}\text{F}$ -FDG PET is often successful in locating the source of infection or inflammation when conventional radiologic techniques fail to do so. Possible indications of  $^{18}\text{F}$ -FDG PET are fever of unknown origin, suspicion of metastatic infectious foci and therapy response monitoring of various inflammatory diseases.

In conclusion, nuclear medicine has a lot to offer in visualization of infectious and inflammatory foci. This, however, cannot be achieved without good collaboration between nuclear medicinists, technologists, hotlab staff, (radio)pharmacists and radiochemists. Moreover, ongoing research (in both experimental laboratory as well as clinical settings) is necessary to warrant future development of new radiolabeled compounds and to assure the central role that nuclear medicine has become to play in the exciting field of infectious and inflammatory diseases.

#### References

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