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# Radionuclide Imaging of Infection and Inflammation in Children: a Review

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**With the exception of radiolabeled monoclonal antibodies, antibody fragments and radiolabeled peptides which have seen little application in the pediatric population, the nuclear medicine imaging procedures used in the evaluation of infection and inflammation are the same for both adults and children. These procedures include (1) either a two- or a three-phase bone scan using technetium-99m methylene diphosphonate; (2) Gallium 67-citrate; (3) in vitro radiolabeled white blood cell imaging (using $^{111}$Indium-oxine or $^{99m}$Technetium hexamethyl-propylene-amine-oxime–labeled white blood cells); and (4) hybrid imaging with $^{18}$F-FDG. But children are not just small adults. Not only are the disease processes encountered in children different from those in adults, but there are developmental variants that can mimic, but should not be confused with, pathology. This article discusses some of the differences between adults and children with osteomyelitis, illustrates several of the common developmental variants that can mimic disease, and, finally, focuses on the increasing use of $^{18}$F-FDG PET/CT in the diagnosis and response monitoring of children with infectious and inflammatory processes. The value of and need for pediatric specific imaging protocols are reviewed.**

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## Introduction

Despite the current reliance on cross-sectional and other anatomical imaging modalities, radionuclide scintigraphy continues to play a pivotal role in the evaluation of infection and inflammatory processes in children. Available radionuclide tests include technetium-99m methylene diphosphonate bone scan ($^{99m}$Tc-MDP), gallium scan ($^{67}$Ga), in vitro radiolabeled leukocytes (WBCs) and, more recently, $^{18}$F-FDG. Their mechanisms, strengths, limitations, and respective roles in the evaluation of infection and inflammatory processes in children are outlined below.

$^{99m}$Tc-MDP, the most widely used radionuclide agent for skeletal scintigraphy, binds to the hydroxyapatite crystal within the bone matrix, with uptake dependent on blood flow and the rate of new bone formation.[1,2] Its role in infection (which increases bone turnover and thus uptake on bone scan) is limited to diagnosing acute and chronic osteomyelitis and distinguishing osteomyelitis from cellulitis and septic arthritis.[3] While sensitive and specific in uncomplicated osteomyelitis, this test is less useful in those with preexisting conditions such as fracture or orthopedic hardware.[4]

$^{67}$Ga was one of the earliest radiotracers used in the evaluation of infection. Several mechanisms govern the uptake of $^{67}$Ga at sites of infection or inflammation. Almost 90% of circulating $^{67}$Ga is transferrin bound within plasma. In infectious processes, not only is there increased blood flow but also there is increased vascular membrane permeability leading to increased delivery and accumulation of $^{67}$Ga at sites of disease involvement. Additionally, $^{67}$Ga binds to lactoferrin which is present in high concentrations at sites of infection.[3] Unfortunately, not only does $^{67}$Ga lack specificity, but its use is hampered by long imaging times (24-72 hours); low resolution; high physiological uptake in liver, kidneys, and bowel, which decreases its sensitivity in the detection of pelvic or intra-abdominal infections; and high patient radiation dose.[5] $^{67}$Ga is rarely used in the evaluation of infection in children; in adults, its role is limited to assessment of spinal infection when $^{18}$F-FDG imaging is not feasible.[6] A positron-emitting counterpart to $^{67}$Ga is $^{68}$Gallium ($^{68}$Ga), which when labeled

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with citrate, can be used in the detection of infectious and inflammatory processes, achieving higher spatial resolution than $^{67}$Ga related to the use of PET/CT. Similar to $^{67}$Ga as well as $^{18}$F-FDG, $^{68}$Ga, while sensitive, is not specific and cannot distinguish between tumor and infection.[7] Further investigation into the role of $^{68}$Ga for the imaging of infection and inflammation is warranted.

Leukocytes, the primary mediator of the human immune system, defend the body against invasive microorganisms. Radionuclide labeling and imaging of labeled leukocytes can identify sites of infection or inflammation. The uptake of radiolabeled leukocytes depends on three variables: intact chemotaxis, the type and number of cells labeled, and the cellular component of the inflammatory response.[3] Since neutrophils comprise the majority of labeled WBCs, this test is most useful for neutrophil-mediated processes such as bacterial infections and less useful for viral or parasitic infections which do not elicit a neutrophilic response.[8] Leukocytes can be labeled with either $^{111}$Indium-oxine or $^{99m}$Tc-hexamethyl-propylene-amine-oxime ($^{99m}$Tc-exametazime). While the use of $^{111}$In WBC scanning for infection is prevalent in adults, its use is discouraged in children due to its high radiation burden.[9] Disadvantages of in-vitro labeled white cell imaging include an expensive and labor-intensive labeling procedure, lack of availability, risk to health care workers involved in the handling of blood products, the possibility that severely neutropenic patients may not have sufficient leukocytes for adequate labeling, the large quantity of blood needed for the procedure limiting its use in neonates and young children, and limited success of the procedure for chronic processes.[10] The use of $^{111}$In is further hampered by the long interval required between radiotracer administration and imaging, poor spatial resolution, and, finally, lack of specificity with uptake seen in inflammatory, neoplastic, and infectious processes.[11-14] $^{99m}$Tc-labeled WBC have better gamma camera imaging characteristics leading to improved image resolution as well as the ability to detect abnormalities within a few hours of administration. Disadvantages include instability of the label, short half-life of $^{99m}$Tc limiting its utility in indolent infections, the presence of urinary and colonic activity which may interfere with identification of intra-abdominal and pelvic infections, and lack of specificity, similar to $^{111}$In.[11,14,15]

The utility of $^{18}$F-FDG in the identification of infection and in monitoring its response to treatment continues to evolve, particularly in adults. In children, $^{18}$F-FDG uptake has been reported in a variety of infectious diseases, including osteomyelitis,[16,17] inflammatory bowel disease,[18-20] chronic granulomatous disease,[21,22] fungal infection,[23-27] and vasculitis,[22] as well as in the evaluation of fever of unknown origin in general and when encountered in the pre-liver transplant or post-transplant patient.[28-31]

$^{18}$F-FDG is initially carried into cells by the glucose transport system where it is converted to $^{18}$F-2'-FDG-6-phosphate, which unlike glucose, is then trapped within the cell where it accumulates at a rate proportionate to glucose utilization.[32] Similar to malignant cells, activated inflammatory cells use glucose as a source of energy leading to high FDG accumulation at sites of inflammation and infection. On the molecular level, overexpression of glucose transporter 1 receptors in stimulated neutrophils, leukocytes, and macrophages has been proposed as the mechanism of FDG uptake in inflammatory cells.[33,34]

High spatial and contrast resolution, high target-to-background ratios, short imaging times resulting in the ability to quickly obtain results, precise localization of abnormalities, high sensitivity, high inter-observer agreement, and, when optimized protocols are used, relatively low radiation dose compared to either $^{67}$Ga or radiolabeled WBC imaging are only a few of the advantages of the use of $^{18}$F-PET/CT for the imaging of infection as compared to the conventional nuclear medicine techniques previously used.[10] Limitations include limited availability, relatively high cost, the need for sedation in younger children, and, most important, the inability to reliably distinguish infection from non-infectious inflammation or malignancy.[35]

Despite recent controversies regarding the linear no-dose threshold theory as it relates to the health effects of low-dose radiation exposure as occurs with diagnostic imaging,[36] there is evidence that the radiation-induced risk of adverse health effects is greater in children than in adults.[37-40] Radiation-induced cancer risk is a function of effective dose administered, age, and gender, with females and younger patients more susceptible to radiation-induced cancers. Not only are children more sensitive to radiation than adults, but they have a longer lifespan in which to manifest radiation-induced injury. For these reasons, it remains prudent to evaluate each request for imaging procedures such as nuclear medicine that expose a patient to ionizing radiation and carefully weigh the risks of such exposure against potential benefit. Before imaging, we must ensure that the requested study is the right test, performed using the right dose, for the right patient, at the right time.[41] This is especially important for high dose studies including $^{67}$Ga, $^{111}$In-WBC and $^{18}$ F-FDG PET. When imaging is deemed necessary, it is important to perform the examination to the highest technical standards and use the lowest administered radiopharmaceutical dose that will allow appropriate diagnostic information. With this aim in mind, consensus guidelines for pediatric-specific, weight-based radiopharmaceutical administered activities had been developed,[42-45] harmonized,[46] updated,[47] and shown to have a positive effect on the practice of pediatric nuclear medicine.[48,49] These easily accessed guidelines for radiopharmaceutical administered activities should be used when performing nuclear medicine procedures in children of all ages.

## Musculoskeletal Infections: Conventional Scintigraphic Agents and $^{18}$F-FDG PET/CT

The diagnosis of musculoskeletal infection in children presents an ongoing challenge. Early recognition of musculoskeletal infection in this age group may be difficult or confused with pathologies such as tumor or trauma.

### Acute Osteomyelitis

Osteomyelitis, an infection of cortical bone and bone marrow by pyogenic organisms, is more common in children than in