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PET/CT and SPECT/CT for Infection in Joints and Bones: An Overview and Future Directions

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Infections of the bones and joints, if misdiagnosed, may result in serious morbidity and even mortality. A prompt diagnosis followed by appropriate management may reduce the socio-economic impact of bone and joint infections. Morphologic imaging such as ultrasound and plain radiographs form the first line investigations, however, in early infections findings may be negative or nonspecific. Nuclear medicine imaging techniques play a complementary role to morphologic imaging in the diagnosis of bone and joint infections. The availability of hybrid systems (SPECT/CT, SPECT/MRI, PET/CT or PET/MRI) offers improved specificity with ability to assess the extent of infection. Bone scans are useful as a gatekeeper wherein negative scans rule out sepsis with a good accuracy, however positive scans are nondiagnostic and more specific tracers should be considered. These include the use of labeled white blood cells and antigranulocyte antibodies. Various qualitative and quantitative interpretation criteria have been suggested to improve the specificity of the scans. PET has better image resolution and ^{18}F-FDG is the major tracer for PET imaging with applications in oncology and inflammatory/infective disorders. It has demonstrated improved sensitivity over the SPECT based tracers, however, still suffers from lack of specificity. ^{18}F-FDG PET has been used to monitor therapy in bone and joint infections. Other less studied, noncommercialized SPECT and PET tracers such as ^{111}In-Biotin, ^{99m}Tc-Ubiquicidin, ^{18}F-Na-Fluoride, ^{18}F-labeled white blood cells and ^{124}I-Fialuridine to name a few have shown great promise, however, their role in various bone and joint infections has not been established. Hybrid imaging with PET or PET/MRI offers huge potential for improving diagnostics in infections of the joints and bones.

Introduction

Nuclear medicine has evolved from the first rectilinear scanner and anger camera to the present-day hybrid imaging involving the merging of functional images with anatomical images by integrating single photon emission tomographic (SPECT) and positron emission tomography (PET) with computed tomography (CT) or magnetic resonance imaging (MRI) modalities. This fusion has combined the inherently unique and independently excellent properties of the imaging technologies to form a new more formidable modality. When using hybrid imaging, the sensitivity and specificity of vast array of clinical applications has improved, and the reader has a higher diagnostic confidence. Further benefits of hybrid imaging include patient convenience as a single session provides a whole-body survey with anatomical and functional data, individualization of medicine and the ability to monitor interventional procedures.

SPECT systems integrated with CT have been available since the beginning of the century and were conceived primarily for the purpose of providing routine CT-based attenuation and scatter correction of SPECT data, however the benefits led to the adoption of this combination of CT for PET systems.[1] In the year 2000, Times Magazine voted PET/CT as the medical invention of the year, and we have seen a

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tremendous growth and uptake of this modality in clinical practice. Alongside the invention, there has been an equally significant boom in the development of tracers that match the capabilities of these technologies.

Despite the advances in the technology and imaging equipment, infections of the bones and joints still pose a challenge for clinicians as various investigations including imaging studies are often employed prior to arriving at a diagnosis. An accurate diagnosis is pivotal to patient management and ensuring precision medicine, where the right patient gets the right treatment at the right time. Radiographic examinations are generally the first line of investigations, however, often provide insufficient information to make a diagnosis of infection. Other morphologic (CT and MRI) and nuclear medicine imaging investigations are considered when radiographs fail to confirm the pathology. Several infection and orthopedics societies have formulated guidelines and appropriate use criteria (ACR) to guide clinicians on the most appropriate imaging modalities in the investigation of infections of the joints and bones.

Bone scintigraphy forms the backbone of musculoskeletal imaging in nuclear medicine, and it takes advantage of the increased bone turnover in most skeletal pathologies including infection. It is often used as a screening tool because a negative scan almost invariably excludes infection, at least this applies in most infections in nonviolated bone. The added value of SPECT/CT in patients with musculoskeletal infections is unquestionable. When added to a bone scan, the specificity moved from 50% for three phase bone scans alone to 86% with the addition of SPECT/CT.[2] Labeled white blood cells (WBCs) techniques using Technetium-99m (^{99m}Tc) or Indium-111 (^{111}In) provide improved specificity over bone scintigraphy, however, may be of limited value in certain pathologies such as spondylodiscitis. Labeled WBCs especially, ^{99m}Tc labeled require the handling of blood products, prolonged imaging times (24-hour imaging) and have fallen out of favor. It was out of this quandary that antigranulocyte antibodies and their smaller fragments were borne, however, they too found low uptake in general practice due to their lack of availability and inherent limitations (eg, production of human antimurine antibodies—HAMA). Specific radiolabeled bacterial tracking or targeting and antibiotics have also been explored, however, more work is needed. ^{18}F-FDG is the mainstay tracer for PET in most clinical applications and its ability to image inflammation, infection and malignancies has been exploited. While its use in many applications is a strength, it is also a weakness as it implies nonspecificity. Other PET tracers including ^{18}F-labeled WBCs and ^{67}Ga-citrate, ^{123}I-fialuridine have been investigated for utility in musculoskeletal infections with variable success.

This review aims to provide an overview of the value of SPECT/CT and PET/CT in the imaging of joints and bone pathologies. There have been ongoing efforts in the area of infection imaging with various SPECT and PET tracers investigated for applications in various infectious processes. These various infection imaging tracers used in SPECT/CT and PET/CT imaging will be discussed followed by the clinical applications especially in the most encountered clinical scenarios or what we felt are the major bone and joint infections.

SPECT/CT and PET/CT Radiopharmaceuticals for Infection Imaging in Joints and Bones

SPECT Radiopharmaceuticals

^{99m}Tc-Diphosphonates. ^{99m}Tc-diphosphonates form the backbone agents for bone scintigraphy in nuclear medicine. The mechanism of uptake is by chemical adsorption onto and into the crystalline structure of hydroxyapatite crystals, which is influenced by the blood flow to the area as well as the rate of new bone formation.[3] The three-phase bone scan is often used in inflammatory or infective bone pathologies and can detect changes in the bone from as early as 2-3 days following the insult, in this case, infection.[4] While sensitive it is not specific, as any condition that results in high bone turnover may result in increased uptake of tracer. The three phases consist of a perfusion phase, soft tissue phase and a delayed (2-4 hours) skeletal phase. Positivity on all three phases of a bone scan is associated with acute bone infections, whereas positivity on the first two phases is more likely suggestive of soft tissue infection. Some investigators have proposed adding a delayed (24 hour) image to make a fourth phase and the justification behind rests on the premise that in normal bone, uptake of diphosphonates should remain stable or decrease while in bones afflicted by infection or tumors, the uptake should continue to increase.[5] Logistically, this is not favorable to the patients and staff and the addition of SPECT/CT has improved the specificity of bone scans.

Gallium-67 Citrate. In an effort to overcome the limitations of bone scans in diagnosing musculoskeletal infections, Gallium-67 citrate (^{67}Ga-citrate) was investigated. In most sites of inflammation and infection there is increased blood flow and increased vascular membrane permeability and this is the basis of accumulation of ^{67}Ga-citrate at these sites. Other mechanisms of accumulation at infective sites include binding to lactoferrin, complexing to bacterial siderophores, and direct bacterial uptake. The advantage of this tracer is that it can still be utilized in patients with leucopoenia as the uptake is multifactorial and not solely dependent on white blood cell accumulation.[6] The addition of bone scintigraphy may assist in diagnosing infections, where incongruent findings of increased ^{67}Ga-citrate uptake more intense or spatially dissimilar to bone scintigraphy was in keeping with infection. Despite the enhancements offered by the addition of SPECT/CT in improving the specificity of this tracer, the need for delayed imaging (>24 hours), high radiation dose and suboptimal image quality have seen a decline in the use of this tracer for infection imaging.[7] This was further compounded by the addition of new tracers to the armamentarium of available tracers and techniques for infection imaging. With that said, it should still be noted that while labeled WBC scanning

supersedes ^{67}Ga-citrate for infection imaging in numerous clinical settings, ^{67}Ga-citrate is still the tracer of choice for suspected spine infections for SPECT applications.

Labeled White Blood Cells. The evolution of infection imaging saw the introduction of the concept of white blood cell labeling into clinical medicine over four decades ago. The most studied and utilized isotopes for labeling WBCs are ^{111}In-oxyquinoline and ^{99m}Tc-exametazine. In acute inflammation/infections, the predominant cells are the neutrophils which are attracted to the site of inflammation/infection by chemotaxis. Neutrophils also happen to be the highest number of cells tagged when performing in vitro labeling of WBCs, therefore, this technique is sensitive for processes in which these cells predominate such as acute bacterial infections. There should be ≥2000 circulating WBCs per microliter in order to achieve images of an acceptable diagnostic quality.[8,9] There are several advantages and disadvantages to using the different isotopes available and these determine the clinical application and use (Table 1).

Labeled WBCs accumulate in areas of infection as well as activated bone marrow which is usually the case in most infections involving violated bone. This lack of specificity may be improved by the addition of bone marrow imaging performed with ^{99m}Tc-sulfur colloid. This complementarity is based on the principle that both will accumulate in sites of activated bone marrow, however, ^{99m}Tc-sulfur colloid will not localize in sites of infection. Therefore, a positive scan will be one that demonstrates incongruencies in the distribution between labeled WBCs and ^{99m}Tc-sulfur colloid in that a positive uptake on WBC scan without corresponding uptake on bone marrow imaging is positive for infection.[8] An alternative to combined WBCs and bone marrow imaging is the dual time point imaging at 4 and 20-24 hours with time decay-corrected acquisition followed by visual and semiquantitative analysis proposed by Glaudemans et al. (Figs. 1-3).

With the visual analysis, the diagnostic accuracy of 94.5% was achieved.[10] The major limitations of labeled WBCs are that they cannot be performed in neutropenic patients and have found limited use in patients with spinal infections.

Labeled Antibodies. The need for handling of blood products and cell separation when performing in vitro white blood cell labeling, led to the search for simplified, yet accurate ways of tracking infections. Monoclonal murine antibody against human granulocytes (Besilesomab) labeled to ^{99m}Tc have been investigated since the late 1900s. Nonspecific cross-reacting antigen 95, NCA-95 is found in the cytoplasm and cell membrane of granulocytes and granulocyte precursor cells.[11] The antibody recognizes this NCA-95 and binds on the epitope. The in-vivo binding of this molecule to granulocytes is >90% and there is no altered function of the granulocytes.[12] The published data indicate that mixed results with some authors reporting an improved sensitivity and others not.[11,12] When it comes to the specificity, however, there was an agreement that specificity is relatively lower than that of ^{99m}Tc-HMPAO- labeled white blood cells.[11,12] The risk associated with the development of a HAMA response with repeated imaging led to probes into using fragments or smaller peptides that will still bind the antigen. ^{99m}Tc-Sulesomab is a 50kDa fragment antigen binding (Fab') portion of IMMU-MN3, an IgG1 class murine monoclonal antibody that binds to normal cross-reactive antigen-90 on leucocytes. Several studies have demonstrated the value of ^{99m}Tc-Sulesomab for imaging infections with variable sensitivities (76%-90%) and specificities (75%-87.5%).[13-17] The general consensus among them all is that it is easier to perform (no tedious labeling procedure) and infections may be detected as early as 1 hour postimaging obviating delayed imaging. One disadvantage of ^{99m}Tc-Sulesomab is that it also presents with nonspecific uptake, therefore it may not differentiate sterile inflammation from infection.

^{99m}Tc-Ubiquicidin. Ubiquicidin (UBI) is a 59 amino acid residue antimicrobial peptide. It was initially discovered in cytosolic extracts of the murine macrophages.[18] Antimicrobial peptides are a category of small peptides that exist in nature, and they form an integral part of the innate immune system of different organisms. They have a wide range of inhibitory effects against bacteria, fungi, parasites, and viruses.[19] These peptides do not have an affinity for the host organisms cells therefore, they are only cytotoxic to pathogenic bacteria, viruses, yeasts, and fungi and as such are involved in wound healing, apoptosis, and immune modulation.[18] This makes antimicrobial peptides ideal targeting molecules for infections especially where the suspected pathogen is unknown. Owing to their characteristics, these peptides should be able

Table 1 Differences Between ^{111}In-Oxyquinoline and ^{99m}Tc-Exametazine Labeled WBCs

Properties	^{110}IN-Oxyquinoline	^{98m}Tc-Exametazine
Imaging time	Delayed imaging is required (18-30 hours)	Imaging may be performed within 4 hours
Biodistribution	Stable biodistribution even after 24 hours	Eluted from WBCs, therefore distribution variable (kidneys and hepatobiliary excretion
Clinical applications	May be used for imaging abdominal pathologies/infections	Limited applications in abdominal pathologies/ infections because of the biodistribution
Timing of complementary marrow imaging	Complementary bone marrow imaging may be performed simultaneously	Complementary bone marrow imaging must be delayed by 2-3 days
Image quality	Low resolution images	High resolution images
Radiation dose	High radiation dose	Low radiation dose

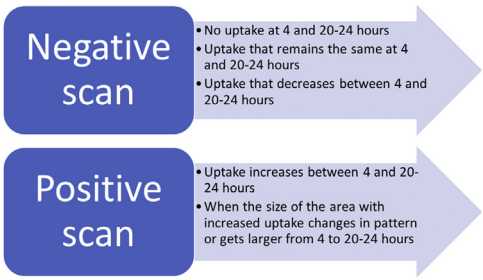

Figure 1 Diagrammatic illustration of the visual analysis interpretation criteria when using early (4 hours) and delayed (20-24 hours) white blood cell scan imaging as proposed by Galudemans et al.[10] for the diagnosis of infection.

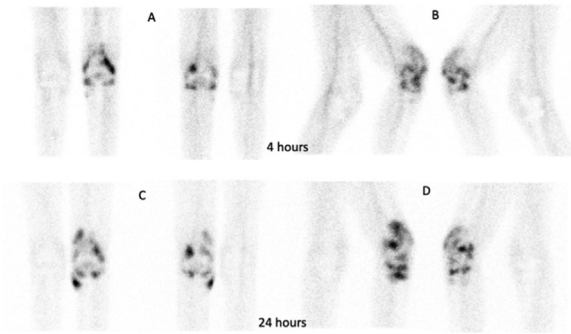

Figure 2 A 66-year-old male with previous history of bilateral knee replacement. Also known with sero-positive rheumatoid arthritis. He presents with a chronic draining sinus. A ^{99m}Tc-HMPAO white blood cell scan performed at 4-hour postinjection revealed (A and B) intense uptake in the left knee prosthesis involving both the femoral and tibial component. Images acquired at 24 hours post-tracer injection revealed intensification of areas seen on the 4-hour scan as well as change in the shape and pattern of uptake which are in keeping with infection.

to distinguish sterile inflammation from infections. Preclinical work with UBI labeled with ^{99m}Tc, demonstrated higher affinities for bacterial cells than for human WBC's.[20,21] In a biokinetic study, the authors found fast blood clearance with a mean residence time of 52 minutes with renal clearance

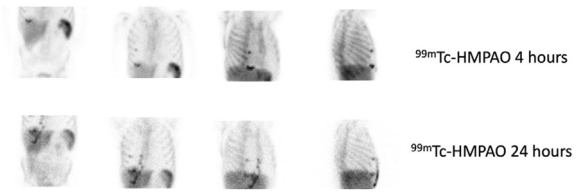

Figure 3 A 65-year-old male with a history of a chainsaw injury to the lower aspect of the anterior chest wall a year ago. He now presents with a draining sinus from the skin wounds at the injury site. A ^{99m}Tc-HMPAO scan was performed to assess for osteomyelitis. There is a focal area of tracer accumulation in the right chest wall at the anterior end of the fifth and seventh ribs. On the 24-hour images, there is a change in the spatial distribution of the uptake in the seventh rib with other new areas of focal uptake in the right border of the sternum tracking inferiorly to the region of the liver. Findings were in keeping with an active infection. A SPECT/CT would have been of value to correctly localize the uptake seen.

of ±85% of the injected activity at 24 hours after administration. An average target to nontarget ratio of 2.18 ± 0.74 was seen in lesions that were considered positive on the scan at 2 hours. The mean absorbed radiation dose was 0.13 mGy/MBq for the kidneys.[22] A meta-analysis of the diagnostic value of ^{99m}Tc-UBI in infectious processes by Ostovar and colleagues found that ^{99m}Tc-UBI 29-41 had an overall accuracy of 93.7% in differentiating infection from noninfectious processes in patients with various musculoskeletal and soft tissue pathologies (Fig. 4).[23] While ^{99m}Tc-UBI cannot replace radiolabeled WBC imaging, it may be considered in patients with leukopenia. A later systematic review of 15 clinical studies found an overall accuracy of 94.4% (95% confidence interval: 91.6%-97.2%).[24] The use of the CT component in SPECT further improves the accurate assessment and extent of infection which has implications on the management.[25] The advantage of ^{99m}Tc-UBI is that it can be used for monitoring response to antibiotic therapy because the uptake represents the number of viable bacteria.[23]

^{99m}Tc-Ciprofloxacin. While the above-mentioned infection imaging methods can detect inflammation or infection, they cannot discriminate between an infectious vs noninfectious inflammatory response (eg, bacteria, viruses, fungi, yeasts, etc.). Direct bacterial binding has been attempted with the radiolabeled antibiotic, ^{99m}Tc-Ciprofloxacin (Infecton). Its

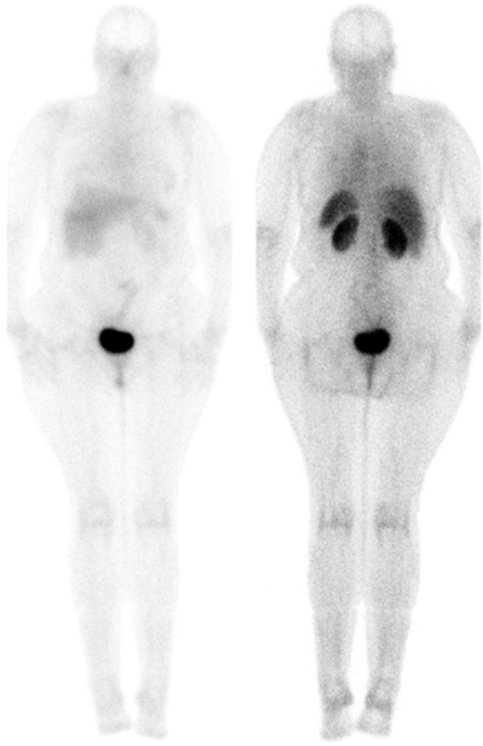

Figure 4 A 70-year-old female with a history of spinal surgery. Now presents with back pain and raised inflammatory markers. ESR =; WCC =. A ^{99m}Tc-UBI scan was performed to assess for possible spine infection postsurgery. The whole-body anterior and posterior images demonstrated no focal areas of increased abnormal uptake of tracer to suggest an acute spinal infection.

application in imaging various infections of the musculoskeletal system include prosthetic joint infection (PJI), osteomyelitis and spinal infections.[26-30] This tracer was found to perform better than labeled WBCs in imaging spinal infections, however, caution should be applied in postoperative spines (<6 months).[29,31,32] A negative scan may be seen in the setting of previous or current antibiotic therapy and therefore it has been proposed as a treatment monitoring tool.[30,33] The clinical utility of this tracer is still uncertain.

^{111}In-Biotin. Vitamin H or B7, also known as Biotin, plays an important role in glucose metabolism, is a growth factor used by many bacteria and binds to avidin.[34] The procedure involves two steps in which ^{111}In-Biotin is injected initially followed by administration of avidin 4 hours later. There is a high target to background ratio because as soon as the ^{111}In-Biotin-avidin complex is formed, it is quickly cleared from the normal tissues and kidneys. While it showed potential in imaging spinal/vertebral infections, most of the studies were in the late 1990s or early 2000s with no apparent clinical adoption or impact post this period.[35-37]

PET Radiopharmaceuticals

Fluorine-18-Fluorodeoxyglucose. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is a glucose analogue. Transport into the cells is facilitated by glucose transporters (GLUT1-5), mostly GLUT 1 and GLUT 3, and once in the cells it is trapped with no further metabolization.[38] The cellular metabolic rate and understandably, the number of glucose transporters determine the uptake of ^{18}F-FDG by WBCs. In most of the inflammatory cells, there is increased numbers and expression of glucose transporters. This makes ^{18}F-FDG a nonspecific tracer as it will accumulate in inflammation, infection or even malignancy. The use of ^{18}F-FDG for infection and inflammation has evolved over the years and has seen a wider range of indications for ^{18}F-FDG in the assessment of musculoskeletal infections. Despite newer tracers for PET imaging, ^{18}F-FDG still remains the tracer of choice in investigation of many inflammatory or infectious conditions. The value of ^{18}F-FDG is in the imaging of chronic infections, spinal/vertebral infections and prosthetic infection, however its specificity in the latter is lower than all other indications.[39] Despite the low specificity in certain indications, the overall sensitivity and specificity was higher than bone scintigraphy and the other nuclear medicine infection imaging tracers.[40]

Fluorine-18-Labeled White Blood Cells (^{18}F-Labeled WBCs). The capability of labeling WBC is made possible with modification of the in-vitro labeling procedure.[41] While the fine details and exact mechanisms of radiolabeling may differ between ^{99m}Tc, ^{111}In, or ^{18}F-FDG, the same principles apply when it comes to the labeling procedure in that autologous white blood cells are withdrawn from the patient, labeled with ^{18}F-FDG in this case and reinjected into the patient. The only other difference is that due to the short half-life of ^{18}F-FDG, delayed imaging is not possible, therefore, false negatives may be seen in infections with low neutrophil counts. The indications studied for bone and joint infections include prosthetic infections and osteomyelitis.[42] In a systematic review and meta-analysis by Meyer et al., the pooled (per-patient based) sensitivity and specificity for localizing infective foci in various organs was 86.3%, and 92%, respectively.[42] Most of the studies in this meta-analysis had small patient numbers <50 and were performed for variable pathologies, therefore need for larger prospective studies exist in order to determine the potential for this tracer to be adopted in clinical practice.

Fluorine-18-Sodium Fluoride (^{18}F-NaF)

The Food and Drug Agency (FDA) approved the clinical use of ^{18}F-NaF in 1972.[43,44] In a similar manner to the ^{99m}Tc-lablled bone scan agent, uptake by the bone is by chemisorption with exchange of $^{18}F^-$ for the hydroxyl ion on the surface of the hydroxyapatite crystals.[45] Most of the tracer is retained by the bone in the first pass with only 10% of the tracer remaining in the plasma after 1 hour.[45] Uptake in the bone marrow is minimal which is a great advantage when imaging infections in violated bone. There are limited studies on the use of ^{18}F-NaF as a possible, viable alternative to traditional infection imaging agents in bone and joint disease.[44,46] While it is considered an upgraded bone scan, the utility in various musculoskeletal infections is limited. This may be due to lack of availability and high costs due to the need for a cyclotron. With the increasing availability of PET scanners, a revisit of the various clinical indications and even newer applications may be seen.

Gallium-68-Citrate (^{68}Ga-Citrate). This is the PET version of the classical ^{67}Ga-citrate which shares a few merits including ease of production and uptake mechanisms which makes it an unspecific tracer for infection imaging. It is obtained from a Germanium-68/Gallium-68 generator with a half-life of almost year and makes for accessibility. The short half-life, superior image quality and reduced radiation dose, sets it apart and make it a potential agent in imaging inflammation in various organs including bone and joint pathologies.[47,48] Unfortunately, it is taken up at sites of inflammation and infection by the same mechanisms as its SPECT forerunner and as such may be seen in areas of inflammation, tumor, or even trauma. Data from a few studies suggest that it may be able to differentiate infection from sterile inflammation in patients with prosthetic joint infections.[49-51]

Iodine-124-Fialuridine. Fialuridine (FIAU) is a substrate of bacterial thymidine kinase that was developed as a therapeutic agent for chronic hepatitis B infection, however, did not proceed beyond phase 2 trials.[52] In infection imaging it is thought to bacteria at the infection site. Other than slight differences, the general biodistribution is similar to that of radiolabeled WBCs and ^{18}F-FDG. There is limited data regarding the use of this tracer in infection imaging with the exception of two studies, one of which was a small trial of 12 participants (six healthy volunteers and 6 postprosthetic patients) that was done in two phases assessing biodistribution and dosimetry followed by sensitivity and specificity in

patients with suspected infection in prosthetic knee or hip.[53] Another small study found that this tracer accurately detected infection in all patients except the control uninfected patient.[54]

Specific Joint and Bone Pathologies

Septic Arthritis. The classic definition of septic arthritis is joint inflammation secondary to an infectious etiology. There has been an increasing trend in the incidence of septic arthritis over the years due to several factors including, but not limited to a rise in infections postorthopedic related procedures, widespread use of immunosuppressants, an ageing population and resistance to conventional antibiotics among a few. It is more common in children than in adults with a preponderance for males between the ages of 2 and 3 years. Neonates, immunosuppressed individuals including those undergoing chemotherapy are at increased risk of developing spontaneous septic arthritis. In the adult population septic arthritis most commonly occurs secondary to introduction of organisms into the joint space following skin infections, joint surgery and intra-articular injections. Older age, rheumatoid arthritis, diabetes mellitus, Human Immunodeficiency Virus and generalized sepsis are also risk factors for septic arthritis in adults.

Microbiologically, the commonest pathogens in septic arthritis are bacteria, however depending on the underlying medical condition and geographic location mycobacteria, fungi, viruses and well as other less common pathogens may be involved. In children *Staphylococcus aureus* is the commonest bacterial pathogen, although the age or age group may have an increased risk to developing septic arthritis from other etiological pathogens such as Group B *Streptococcus*, *Kingella kingae*, gram negative *Bacilli*, *Neisseria gonorrhea*, *Salmonella* species, *Pseudomonas aeruginosa*. The list of offending pathogens is not so different for the adult population with *Staphylococcus aureus* also being the commonest organism in this group.

The anatomy of the joint synovium makes it prone to seeding of infections from hematogenous spread in the setting of systemic infection. It is highly vascularized and lacks a basement membrane.[55] As may have been alluded to earlier, the main routes of entry of pathogens into the joint space is through direct inoculation following trauma or medical intervention such as surgery, contiguous spread from adjacent osteomyelitis, nearby soft tissue infection and hematogenous spread. Proliferation of bacteria leads to an acute inflammatory response which may result in joint destruction mediated by inflammatory cytokines and proteases if not managed promptly.

The diagnosis may be missed in the pediatric population as they present with vague symptoms including fever, irritability, tachycardia, loss of appetite, and anemia, however, older children and adult patients may present with clearer symptoms such as fever, swelling and joint pain with associated limited mobility in the affected limb. It usually affects a single site (monoarticular), however, in the cases of fulminant sepsis, immunosuppression and other comorbid conditions, it may involve more than one site (Fig. 5). The hips, knees and ankles are the commonest sites affected by septic arthritis, followed closely by the elbow joint in the pediatric population.

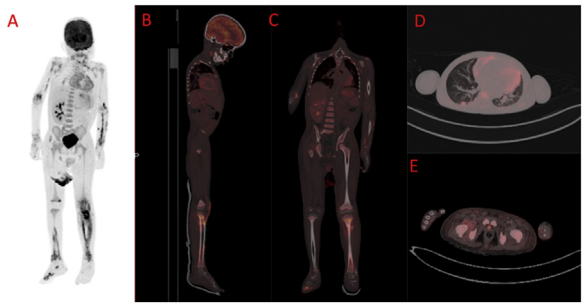

Figure 5 A 6-year-old male with a history of multiple septic emboli. The child was unwell with no echocardiographic evidence of infective endocarditis. Ultrasound revealed a heterogeneous spleen and effusions in the right hip and left knee. ^{18}F-FDG PET/CT was performed to assess for other sites of sepsis. The maximum intensity projection (MIP) images (A), sagittal (B) and coronal (C) images demonstrated disseminated disease involving multiple sites including the pericardium, lungs, joints and skeleton. The lungs demonstrated multiple focal areas of increased uptake (D) and there was a rim enhancing collection with increased intensity in the right hip (E) in keeping with septic arthritis.

First line investigations include biochemical analysis (Erythrocyte sedimentation rate, C-reactive protein and white blood cell counts) and synovial fluid analysis; however, these may be nonspecific and, in some instances, may be negative. Ultrasound and plain radiographs are easily accessible and may reveal joint effusions, widened/reduced joints paces and subchondral bony changes which are late manifestations of the pathology. Ultrasound is also useful in guiding arthrocentesis. MRI is highly sensitive (±100%) and is the modality of choice especially in the pediatric population.[56] Changes on MRI include cellulitis in the soft tissues, cartilage destruction, joint effusions, and bone marrow oedema.[57] While highly sensitive, it is imperfect in that a distinction between infection and noninfectious inflammatory changes cannot be made solely based on contrast enhancement or lack thereof. Nuclear medicine is a viable option in the imaging landscape of septic arthritis, however there is a dearth of studies on the value and utility of these functional imaging methods for diagnosing septic arthritis.

SPECT/CT and PET/CT in Septic Arthritis

In comparative study of ^{99m}Tc-labeled MDP and nanocolloid for diagnosing osteomyelitis and septic arthritis, the overall sensitivity, specificity and accuracy for ^{99m}Tc-MDP bone scans was higher than that of ^{99m}Tc-nanocolloid marrow imaging (100%, 85%, and 94% vs 90%, 59%, and 76%, respectively).[58] The authors concluded that nanocolloid is not a specific investigation and therefore cannot be recommended as an adjunct to bone scans. On three phase bone scan, the typical findings of septic arthritis are increased uptake in the first two phases while the delayed phase may show increased activity at the articular surface or normalization of uptake.[9] The panel members of the ACR

appropriateness criteria for investigating patients with suspected osteomyelitis, septic arthritis and soft tissue infection, did not include nuclear medicine imaging as subsequent investigations in patients with suspected septic arthritis where radiographs are normal or suggestive of joint effusion or soft tissue swelling.[59] Palestro et al. also released an appropriate use criteria document for musculoskeletal imaging in nuclear medicine and they also do not recommend the routine use of bone scans in cases of suspected septic arthritis unless as a "rule out" test because of its high sensitivity.[60] In fact, they only recommend the use of combined labeled WBCs/bone scan or labeled WBCs/marrow imaging if there is a suspicion of superimposed osteomyelitis.[60] In cases of suspected septic arthritis with arthroplasty or other implanted intra-articular surgical hardware, the panel deemed three phase bone scan, labeled WBCs scans and ^{18}F-FDG PET/CT as alternatives to CT and MRI because of the hardware artifacts that may impact reporting of the latter modalities.[59]

^{18}F-FDG accumulates in sites of inflammation and infection through the same mechanism, therefore, its role in imaging septic arthritis may be limited as it is unlikely to differentiate between the various inflammatory pathologies such as rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.[61,62] Except for a few case reports or small-scale studies, there is limited data regarding the use of ^{18}F-FDG PET for imaging septic arthritis.

Periprosthetic Joint Infection. In the adult population the commonest cause of joint pathology is due to postarthroplasty complications which may include loosening of implant or periprosthetic joint infection. While loosening, heterotrophic ossification, and fracture are common complications postarthroplasty, prosthetic joint infection is by far the most difficult to diagnose and manage and may have far reaching effects if not detected early. It is therefore imperative that prosthetic joint infections are detected promptly to minimize economic impact (for both patient and the health care system), patient morbidity and maintain acceptable function. By virtue of the invasiveness of the procedure it is not surprising that most of the organisms are introduced during surgery. The other mechanisms by which infection or infectious organisms can be introduced is by contiguous spread from an adjacent area of infection and the hematogenous spread.

Numerous classification schemes exist for periprosthetic joint infection, and these range from simple to more complex classifications. Most of these schemes incorporate the time of setting in of the suspected infection from the time of surgery and some incorporate the host factors. An example of a simple classification is that popularized by Tsukuyama et al. who classified the infection as early, delayed or late with an early infection considered as that occurring within 3 months of the surgery, while a late infection is considered as that occurring 1 year postoperatively.[63] Of note is that these schemes are related to the offending microorganism and the method of introduction. Early and delayed infections are thought to be due to virulent and less virulent organisms, respectively, introduced at the time of surgery; while late infections are thought to be due to hematogeneous spread, however, may also be due to particularly indolent infection introduced at the time of surgery.

The clinical presentation may vary depending on multiple factors including the host immune response, joints involved and the virulence of the organism. Fever cannot be considered a characteristic symptom as its presence is variable with less than half of patients displaying this symptom, except in the instance of hematogeneous spread as a result of systemic bactaremia.[64] The vast majority (±90%-100%) of the patients presents with pain and joint swelling and draining sinus are

The diagnostic pathway may be challenging and should involve a multidisciplinary team approach involving orthopedic surgeons, internal medicine physicians and imaging specialists (radiologists and nuclear physicians). A thorough history and physical examination of instrumental in directing further investigations and deriving a diagnosis. The diagnosis is reached having considered the symptomatology, signs, biochemical inflammatory markers, culture and synovial fluid analysis. There are several diagnostic criteria from various societies such as Infectious Disease Society of America (IDSA) and Musculoskeletal Infection Society (MSIS) involved in managing patients with periprosthetic joint infections. The criteria for diagnosing periprosthetic joint infection (PPJI) have major/definitive criteria as well as minor/supportive criteria.[65] A commonality among the different societies' criteria is that a sinus tract communicating with the prosthesis and identical micro-organisms isolated from two or more cultures are conclusive evidence of a PPJI.[65]

The clinical practice guidelines by the IDSA recommend plain radiographs as a first line imaging investigation in all patients suspected with PPJI and discourage the routine use of bone scintigraphy, white cell scans, PET, CT or MRI.[66] Contrary to this recommendation, the role of imaging, specifically nuclear medicine imaging with bone scan and white blood cell labeling is recognized and included in the definition of PJJI by only one society, namely, the World association Against Infection in Orthopaedics and Trauma (WAIOT).[67,68] Similarly to the native joint septic arthritis work-up, ultrasound may play a role in assessing for joint effusions and guiding interventional procedures such as joint aspirations.[69,70] A negative radiograph cannot confidently rule out infection in view of its lack of the sensitivity and specificity and therefore other imaging modalities may be considered. CT and MRI suffer from artifacts related to prosthesis, however, when effective implant-related artifacts are subtracted from the CT images, this can provide an accurate assessment of bone architecture.[71,72] MRI is excellent in assessing soft tissues adjacent to the prosthesis and while not specific may help in identifying other causes of joint pain or presenting symptoms.[73]

SPECT/CT in Prosthetic Joint Infections

While they are not routinely employed, nuclear medicine investigations are useful in the assessment of patients with suspected PJI.

Early postoperatively, there is increased bone mineral turnover with resultant increased uptake of ^{99m}Tc-diphosphonates. This very fact makes bone scintigraphy an unspecific tool to confidently confirm infection, however, it is an excellent test to rule it out. A three-phase bone scan is typically performed with increased perfusion, vascularity and uptake considered as highly diagnostic for infection. The combination of SPECT and CT allows for comprehensive assessment of the prosthesis incorporating the metabolic changes with the anatomical abnormalities to better discriminate the various causes of pain postprosthesis. The CT component may reveal areas of lucency with associated periosteal reaction with corresponding increased tracer uptake.[74] Other soft tissue changes in keeping with infection on CT include joint distension, fluid-filled burse and surrounding collections in muscles.[74] Pain is the most common presenting symptom and some groups have proposed a classification system of the SPECT/CT findings in patients with total hip arthroplasties as a way of standardizing the reporting.[75,76] The classification system entails assigning a number to the different components of the total hip replacement in a similar manner to the radiological classification.[75-77] Another group looked at measuring ratios that define normal vs abnormal uptake and found that elevated ratios in prostheses that are less than 12 months and 24 months for the acetabular compartment and femoral compartment, respectively, may represent normal periprosthetic activity. Therefore, the scans should be interpreted with caution and correlated with all the relevant history. Similarly, Pelosi et al. looked at ratios to define a threshold above which the findings are in keeping with PJI. In their work, they drew a region of interest over the prosthesis and the left iliac crest (reference tissue) on early and delayed imaging and considered positivity as an increase in the ratio of >10% from early to late imaging.[78] When imaging with ^{18}F-FDG, semiquantitative parameters such as maximum, mean and peak Standardized Uptake Value SUVmax, SUVmean, and SUVpeak have been utilized to aid the visual interpretation and to assist in classification of the findings. Similarly, these semiquantitative parameters may be applied in SPECT/CT imaging. Yama et al. found a statistically significant difference in the SUVmax and SUVpeak of patients with neutrophilic PJI and those without, on both the early (blood pool) and late phase (delayed).[79] With the exception of the ratios (defining normal vs abnormal uptake) and semiquantitative parameters (SUVmax and SUVpeak), the other classification systems cannot be generalized to investigations pertaining to the knee arthroplasties. There is no one method that is preferred over another, however, the easier a classification system is to perform, the higher the likelihood of adoption into clinical practice, therefore, thus far, the ratios and the semiquantitative measures offer promise as the others require detailed and extensive knowledge of CT interpretation. SPECT/CT changed the diagnosis and treatment plan in 16% of patients and as excepted performed better than planar imaging (k value; 0.717 vs 0.477, respectively). Furthermore, both planar/SPECT only imaging and SPECT/CT performed better in knee prosthesis than in the hip prosthesis, with improved diagnosis in the acetabular component more than the femoral component in hip prosthesis.[80]

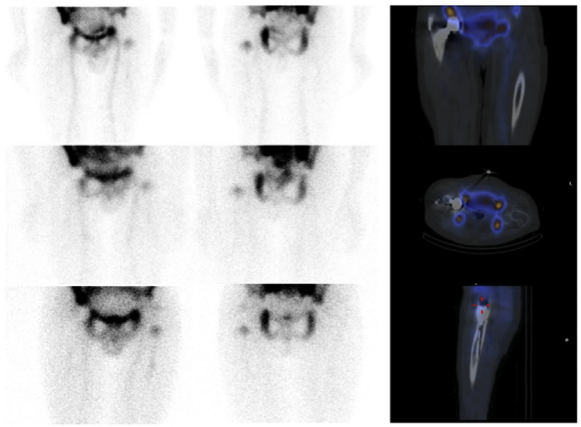

Figure 6 A 52-year-old male with a previous history of right total hip replacement of 14 years who presented with painful right hip. Biochemistry: Normal. X-ray: signs of loosening between cement/implant and cement/bone interface. A ^{99m}Tc-HMPAO scans performed at 3 (A, B) and 24 hours (C, D) and a ^{99m}Tc-nanocolloid scan (E, F) performed did not demonstrate any focal abnormal uptake of tracer. The SPECT/CT (G-I) acquired at 3 hours post-tracer injection of ^{99m}Tc-HMPAO confirmed the above. The findings were in keeping with aseptic loosening of the right hip prosthesis.

While labeled WBCs may be performed on their own with a dual phase protocol as described earlier, or the addition of SPECT/CT to improve the specificity (Fig. 6), because of the presence of activated marrow in most cases of prosthesis, additional marrow imaging may be necessary. The addition of SPECT/CT contributed significantly to the clinical management in almost two-thirds (59.4%) of the patients with a sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of 100%, 90.1%, 100%, and 88.2%, respectively.[81] Interestingly the sensitivity and NPV remained the same on both planar and planar with SPECT/CT, while the largest impact of SPECT/CT is on the specificity and PPV (planar: 59.1% and 62.5% vs planar plus SPECT/CT: 90.1% and 88.2%).[81] In another study SPECT/CT was able to differentiate soft-tissue from skeletal involvement in patients with orthopedic implants as well as osteomyelitis.[82] Furthermore, it helped distinguish synovial infection without involvement of the prosthetic component in knee prosthesis. The value of SPECT/CT has been documented with the use of various other infection imaging tracers.[27,83]

PET/CT in Prosthetic Joint Infections

The many advantages of ^{18}F-FDG have been mentioned previously and although, it has many advantages that supersede those of SPECT imaging, it is unclear whether it will provide diagnostic information that is superior to that of labeled WBCs. Image analysis includes visual and semiquantitative measures, however, there are no accepted thresholds for diagnosing PJI. Visual analysis of uptake patterns is the most

reported criteria used on 18F-FDG PET/CT scans to diagnose PJI.

In a meta-analysis by Verbene et al., ^{18}F-FDG had a higher specificity than bone (84% vs 56%) but lower than in-vitro or in-vivo labeled WBCs (95% and 93%) for diagnosing infections in knee arthroplasties.[84] Based on their analysis, bone scintigraphy is highly sensitive whereas labeled WBCs are highly specific, therefore, ^{18}F-FDG may have limited value in the evaluation of prosthetic joint infections. The same group performed a meta-analysis on the accuracy of imaging techniques in hip arthroplasties. The pooled sensitivity and specificity for ^{18}F-FDG was 86% (95% CI: 80%-90%) and 93% (95% CI: 90%-95%).[85] In another study of suspected infections in hip prosthesis, ^{18}F-FDG PET performed comparably to three phase bone scintigraphy and while it was more specific than conventional radiograph, it was less sensitive.[86] These results should be interpreted with caution because there was heterogeneity in the individual studies. In a more recent meta-analysis, the pooled sensitivity and specificity of ^{18}F-FDG PET for diagnosing both knee and hips PJI was 85% and 86%, respectively. ^{18}F-FDG PET may assist in excluding or confirming periprosthetic hip infection because of it its diagnostic accuracy, however, resources will determine the most appropriate imaging modality to use in various settings and applications.

Other PET tracers that have been used for assessing PJI with variable results and successes include ^{18}F-FDG labeled WBCs, ^{18}F-NaF, and ^{123}I-FIAU. Most of the work on these tracers is based on small sample sizes or in a trial setting with no head to comparisons between these tracers and the more well studied and what is considered "gold standard" tracers for infection imaging in nuclear medicine. What is clear, thus far, is that they also fall short of having characteristics of an ideal infection imaging tracer.

Spondylodiscitis. Vertebral osteomyelitis or spondylodiscitis (SD) as it is more commonly known as an infection of the vertebra including the intervertebral disk. The infection generally starts in the vertebral end plate with spread to the disk. It has a bimodal distribution with two peaks namely in the pediatric patients and elderly >50 years. It is uncommon and only accounts for less than 10% of all skeletal infections. The risk of developing spondylodiscitis from hematogeneous spread or postspine interventions is ±25% and 30%, respectively. Risk factors for SD are similar to most other bone infections and include a history of spinal intervention, bacteremia/septicemia, immunosuppression from any cause, Diabetes Mellitus and malnutrition.[87]

Staphylococuss aureus is the commonest cause of bacterial SD particularly from hematogeneous spread. Other less common bacterial organisms include *Enterobacter* species, *Salmonella*, *Klebsiella*, *Streptococcus*, and *Pseudomonas.* In regions where *human immunodeficiency virus* (*HIV*) burden is high, *Mycobacterium tuberculosis* (Fig. 7) and fungal and or parasitic infections should be considered as the causative organisms.

Like all other skeletal infections, the presentation is not always clear and in the pediatric population it is vaguer with symptoms of refusal to walk, back, neck, or abdominal pain, fever, irritability, malaise, anorexia, and rigidity being reported. The onset of symptoms may be indolent and depending on the site may vary, for example, lower extremity weakness may be the presenting symptom from lower back lesions while dysphagia and torticollis may be reported in cervical spine lesions and patients with cervical or thoracic spine infections had a higher likelihood of having multifocal disease.[88] Anatomically, the lumbar spine is the most frequent site of SD followed by the thoracic and cervical spine with frequencies of 49.5%, 25.8%, and 10.8%, respectively.[89] The morbidity and mortality from multifocal spine infections is higher than from a single site.

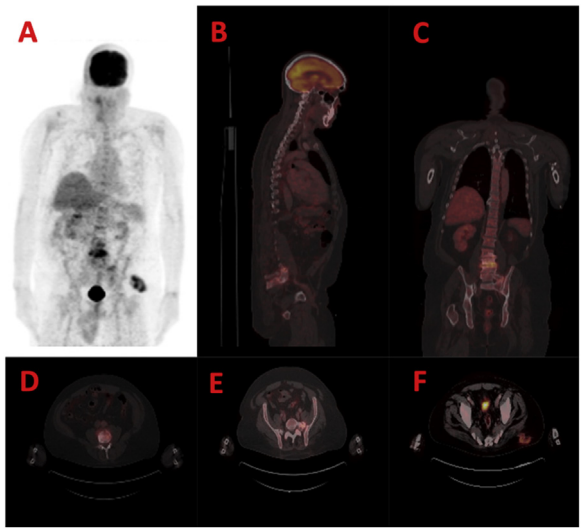

Figure 7 A 62-year-old male with acute onset myelitis with associated back pain. A clinical suspicion of spondylodiscitis was made. Biochemical results were abnormal: ESR = 53 mm/h (normal: 4-10) and WBC = 15.81 (normal: 3.92-10.4). ^{18}F-FDG PET/CT performed revealed uptake in the vertebrae in the lumbar vertebrae (L2-L4) with associated fractures (A-D). Additionally, there was a lytic lesion in the left sacral ala (E) and a left gluteal abscess (F). Findings were in keeping with TB of the spine.

Unlike most other skeletal pathologies, plain radiographs are of limited value in the evaluation of SD, especially in the early phases. Pre- and postcontrast CT is the first line investigation and may reveal calcifications, bone changes and associated para-spinal soft tissue abnormalities. The value of CT is further enhanced by the ability to guide biopsy. Where CT fails is in assessing nerve involvement and disk spaces and this is where MRI is advantageous. MRI has a high sensitivity, specificity and accuracy offering excellent soft tissue contrast. Nuclear medicine procedures are not routinely performed and may play a complementary role in patients that pose a diagnostic dilemma/challenge.

SPECT/CT in Spondylodiskitis

Prior to ^{18}F-FDG, ^{67}Ga-citrate was the SPECT tracer of choice for imaging SD with a sensitivity, specificity, and accuracy of 73%, 61%, and 80%, respectively.[90] To increase the specificity of ^{67}Ga-citrate scans, SPECT/CT may be added. SPECT tracers have limited role in the diagnosis of SD. Labeled WBCs demonstrate photopenic areas in the

spine, bone scans are nonspecific and ^{67}Ga-citrate, while proven to be specific has fallen out of favor as newer tracers hit the market. The interest and availability of this tracer has fizzled.

PET/CT in Spondylodiscitis

According to the ACR appropriate use criteria panel, ^{18}F-FDG PET/CT is the nuclear medicine imaging modality that is most appropriate for imaging SD with or without hardware.[60] The pooled sensitivity and specificity for ^{18}F-FDG PET/CT imaging in SD is 94.8% (95% CI: 88.9%-97.6%) and 91.4% (95% CI: 78.2%-96.9%), respectively with pooled negative likelihood ratio of 0.11 (95% CI: 0.07-0.16).[91] Kloiber et al. proposed a pattern-based criteria for the interpretation of these scans, however this may not be of value in SD from Granulomatous infection as the method of spread is different.[92] In this criterion they considered abnormal uptake as that in bone, soft tissues or spinal canal that was more intense than activity in adjacent uninvolved bone marrow or paraspinal muscles, respectively.[92] Abnormal uptake in the above mentioned regions without an alternative explanation on the coregistered CT is positive for infection regardless of the intensity of uptake. Nonseptic uptake was that due to CT changes/abnormalities such as fractures and focal bone destruction from neoplasms.[92] This criteria does not differ significantly from the qualitative criteria of Hungenbach et al., however they assigned a numerical value to the findings with a score ranging from 0 for no infection to 4 which was suggestive of SD (Table 2).[93]

When it comes to quantitative there is no consensus regarding the cut-off value that will discriminate infectious from noninfectious uptake.

The greatest value of ^{18}F-FDG PET/CT is in the assessment of suspected SD in the postoperative spine. When compared with MRI, ^{18}F-FDG PET/CT displayed superior performance for revealing the extent of infection.[94] This is because morphologic imaging (CT and MRI) is prone to image distortion from metal artifacts, with little to effect on metabolic imaging.

Generally, therapy response is measured as symptomatic response with improvement in the inflammatory markers and no imaging is recommended in patients who appear to have a favorable clinical response.[95] It may take time for treatment changes to be appreciated on MRI and sometimes there may be a paradoxical impression of worsening, therefore, MRI is not useful for treatment response.[96] Qualitative/visual analysis of follow-up ^{18}F-FDG PET/CT studies in patients following initiation or completion of therapy may aid in the assessment of treatment success or failure and therefore guide further management. Fuster and colleagues formulated a response assessment criteria in which they described persistent uptake confined to the margins of a destroyed intervertebral disk following therapy as suggestive of mechanically induced inflammation therefore in keeping with a treatment response, whereas, persistent soft tissue or bone uptake is in keeping with ongoing active infection and no response to treatment.[97,98] Similar to the assessment of PJI, a pattern based assessment as opposed to an intensity based assessment yielded higher specificity (100% vs 55%, respectively) which reduced further on treatments response assessment (100% vs 55%).[99] Studies evaluating the use of ^{18}F-FDG PET/CT for assessing treatment response have utilized different parameters including the change in SUVmax between the pre-, interim, or post-therapy scans.[100-102] In the study with an interim analysis 2-4 weeks after the initiation of antibiotic therapy, a lower SUVmax on the interim scan was predictive of responders with a sensitivity and specificity of 83% and 46%, respectively. Caution should be applied when using ^{18}F-FDG PET/CT or MRI for treatment assessment, there is a higher incidence of uptake that is not of an infective nature or related to the spinal infection, therefore it is necessary to be well equipped with atypical findings to avoid misdiagnosis and inappropriate treatment.

Other less common tracers have been investigated for SD and these include ^{111}In-Biotin, ^{99m}Tc-UBI, and ^{68}Ga-citrate, however, while these offer great potential, there is insufficient evidence to adopt them into clinical practice and as such some of them have not reached commercialization stages.[36,103-105] Perhaps with the increase in the use of hybrid imaging, we will see a resurgence of some of these tracers.

Diabetic Foot Infections. There has been a global trend of a rise in the prevalence of diabetes which is paralleled by a rise in the rate of associated complications such as foot complications, including infections. Diabetes related lower extremity complications including peripheral neuropathy and peripheral vascular disease are predisposing factors to developing infection. Diabetic foot complications are a leading cause of

Table 2 Qualitative Interpretation of ^{18}F-FDG PET/CT Images Proposed by Hungenbach et al.[93]

Score	^{18}F-FDG PET/CT Findings	Diagnosis/Interpretation
0	Normal findings and physiological ^{18}F-FDG distribution	No infection
1	Slightly increased uptake in the inter- or paravertebral region	No infection
2	Clearly increased uptake of a linear or disciform pattern in the intervertebral space	Discitis
3	Clearly increased uptake of a linear or disciform pattern in the intervertebral space and involvement of ground/cover plate or both plates of the adjacent vertebrae	Spondylodiscitis
4	Clearly increased uptake of a linear or disciform pattern in the intervertebral space and involvement of ground/cover plate or both plates of the adjacent vertebrae associated with surrounding soft tissue abscess	Spondylodiscitis

hospitalization and amputations with associated morbidity and mortality as well as health economic burden.[106] A foot infection in any tissue distal to the malleolus in a diabetic patient is considered a diabetes related foot infection.[107] In diabetic patients, a neuropathic ulcer is a predisposing factor to developing sepsis in the foot.

The presence of infection is defined by two or more classical or secondary findings of inflammation or purulence such as redness, warmth, swelling, pain/tenderness or purulent secretions, discolored granulation tissue, or a foul odor. Classification of the severity of the infection determines appropriate management and this classification is broadly graded as mild, moderate and severe with mild disease managed as an outpatient while severe disease requires special imaging procedures and hospitalization and may result in amputation.[108]

Due to the chronic, open nature of predisposing ulcers, diabetic foot infections may be polymicrobial with both aerobic gram positive and negative organisms cultured in these infections. Like all other soft tissue or bone infections, *Staphylococci* are the commonest causative organisms, however obligate anaerobes such as *Preptostreptococcus* and *Bacteriodes* species may be copathogens in ischemic and necrotic wounds.[108,109]

Imaging plays an important role in discriminating soft tissue infection from that involving the bone (osteomyelitis) which is difficult to diagnose and treat, however these are not considered in isolation. Radiographs are appropriate as a first line imaging investigation in these patients, followed up by MRI in patients with soft tissue swelling without an ulcer with suspected early neuropathic arthropathic changes or osteomyelitis. In this setting the ACR considers nuclear medicine with bone scintigraphy, labeled WBC scan or ^{18}F-FDG PET/CT as possible appropriate alternatives to MRI.[110]

SPECT/CT Imaging of Diabetic Foot Infections

While bone scanning is more diagnostic than X-ray in early osteomyelitis, its poor specificity precludes it from being the imaging modality of choice in DFI's. It cannot reliably differentiate neuropathic osteoarthropathy (Charcot's arthropathy) from infections. Historically, a scan that was positive on all three phases was considered pathognomonic for bone infection, however, data has shown that many conditions may mimic osteomyelitis. As in most other bone infections, in the DFI, the value of the bone scan is in excluding an infection as a negative scan almost always excludes the presence of infection. The value of ^{67}Ga-citrate in DFI is not clear. This tracer was initially proposed as a bone scanning agent and it cannot reliably differentiate between infection and neuropathic changes.[111] This tracer is no longer widely utilized and has since been replaced by ^{99m}Tc-labeled WBCs and ^{18}F-FDG. Other investigations evaluating DFI involved the use of ^{111}In-labeled WBC's which had better specificity than bone scan 78% (range: 29%-100%),[112-115] however, in view of the lack of the hybrid systems to accurately localize the site of infection, still presented with many a challenge including poor spatial resolution and lack of bony landmarks. The utility of SPECT/CT improved image analysis and offered better systematic methods of assessing treatment response. Using both the CT and the metabolic information at 2 hours and 20 hours, Vouillarmet et al., the composite score index (CSI) score which incorporates intensity of uptake and stage of bone erosion on CT.[116,117] This score was used in assessing remission after cessation of treatment and it was found that when the duration of antibiotic treatment is driven by WBCs imaging, the remission rate was 84%.[116] There is hematopoietically active marrow in the neuropathic joint/foot which results in labeled WBC accumulation even in uninfected bones. The addition of a marrow scan assists in differentiating between activated marrow and infection in DFI. Simultaneous dual-isotope ^{110}In-labeled WBCs/^{99m}Tc-MDP SPECT/CT and marrow imaging were significantly more accurate than planar imaging and single-isotope SPECT/CT.[118]

PET/CT in Diabetic Foot Infections

A systematic review and meta-analysis on imaging modalities in people with diabetic foot ulcers and in 36 studies, found that MRI and PET had high accuracies that were similar.[119] Either one of these tests may be suitable for imaging osteomyelitis in this patient group.

Some authors have reported high accuracies (81%-96%) for the ability of ^{18}F-FDG PET/CT to differentiate between soft tissue infection and osteomyelitis.[120-122] While many authors have reported on the value of ^{18}F-FDG PET/CT for imaging diabetic foot infections, Familiari and colleagues found a low diagnostic accuracy and despite formulating a criterion for DFI, found that ^{18}F-FDG PET/CT cannot replace WBC scintigraphy in patients with diabetic foot. In their analysis they found that a lesion to background ratio of >2 at 20 hours on the ^{99m}Tc-labeled WBC study, was in keeping with a diagnosis of infection. The ^{18}F-FDG study was considered positive when the SUVmax was >2 on the 1- and 2-hour images. These criteria are not used universally; however, such systems are important for standardizing reporting and communicating. Despite all these efforts, the role of ^{18}F-FDG PET/CT in the diagnosis of DFI is still uncertain and this warrants more large, multicenter investigations.

Future Perspectives and Conclusion. While there have been huge strides in the development of infection imaging agents, there is no tracer that fulfills the criteria for an ideal agent. In view of the complex nature of infections, it is unlikely that such an agent will be found. The existing complement of tracers have demonstrated great clinical value for imaging infections in various organs including joints and bones. Newer imaging probes that have shown great potential in preclinical or small pilot studies form SPECT and PET imaging include other radiolabeled antibiotics beyond Ciprofloxacin such as ^{99m}Tc-isoniazid (TB), antimicrobial peptides (^{99m}Tc-HYNIC-Polymyxin-B), nanoparticles (^{99m}Tc-HPβCD), sugars (^{18}F-Fluorosorbitol) and alcohols (^{18}F-fluoromaltose and ^{18}F-Fluoromaltotriose).[123-129] Despite initial promising results, these potential tracers have not fully entered the clinical arena, this may be due to the presence of biases, lack of standardization in terms of labeling procedures, image acquisition and interpretation. The Appropriate use criteria

document by Palestro et al. further highlights this lack of clinical applicability of most of these tracers as none of these tracers feature as potential options when imaging various musculoskeletal pathologies.[60] While it was not intended for infection imaging, 68Ga-FAPI has been documented in inflammatory sites and its impact or potential role in infection imaging may be explored in the near future.

The advancements in SPECT/CT are important as this is the workhorse of nuclear medicine, and in many departments across the world, it is the only nuclear medicine equipment available. Improvements on the collimators such as the multi pinhole principle, currently in use in preclinical small animal imaging is a promising addition as it promises improved spatial resolution, however one should bear in mind that there is usually a tradeoff between spatial resolution and sensitivity. In orthopedic patients, time on the bed is an important aspect and measures that would reduce this time without compromising the image quality would be welcome. One such possibility is that suggested by Picone et al. in which the detectors are in constant motion during the acquisition.[130] This acquisition reduced the scan time by 25% and furthermore the image quality and signal quantification were preserved.[130] Localizing lesions is just as important as identifying them and the fusion of SPECT and CT has enabled enhanced lesion localization. The spatial resolution of a SPECT camera is limited by the detectors capabilities, and this sparked the interest in the use of semiconductive materials such as cadmium-telluride and cadmium-zinc-telluride (CZT) for detecting ionizing radiation in next generation gamma cameras. They offer increased energy resolution as compared to the traditional Anger camera; however, others have found that primarily the SPECT resolution is improved.[131-133] Another important improvement that has an impact on treatment monitoring is the concept of quantification. The hybrid systems allow for such quantification; however, this area needs more standardization so as to harmonize this.

Advances in PET technology such as the use of silicon photomultiplier tubes and increasing the length in the axial direction have resulted in increased intrinsic sensitivity. Another added advantage of these improvements is shorter scan times and the ability to administer lower radiopharmaceutical doses. Follow-up of patients for response assessment can be achieved with a reduction in the total radiation received. The development of total body PET can help improve the kinetic analysis of the various tracers under investigation. Patients with metal hardware have metal artifacts which may impede adequate reporting. The addition of metal-artifact reduction to the CT component, has improved the visual interpretation of scans especially in patients with metal implants/hardware or prosthesis.

While metabolic imaging offers increased sensitivity, the integration of CT and MRI to nuclear medicine imaging systems offers solutions to issues around specificity and localization of metabolic tracers. This amalgamation offers some solutions and improvements in the diagnostics of complex pathologies. Interest is on the complementarity of PET and MRI systems in the form of integrated PET/MR systems as more systems enter the clinics. The multimodality imaging merges the highly sensitive PET metabolic imaging, and MRI with its high specificity and anatomical detail. This represents an ideal one-stop-shop for imaging of musculoskeletal pathologies including bone and joint infections. To maximize on the benefits of both imaging modalities, administration of a cocktail of tracers, that is, ^{18}F-FDG for PET and Gadolinium-DTPA for the MRI at the same time has been proposed. This will allow for the accurate assessment of the specific biochemical and physiologic target. We anticipate that these hybrid systems will result in the adoption of metabolic imaging in guidelines with incorporation earlier in the diagnostic pathway of infections of the bones and joints. Coupled with this, there is a need for training on these so as to equip ourselves with the skills to better interpret hybrid imaging studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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