Appropriate Use Criteria for the Use of Nuclear Medicine in Musculoskeletal Infection Imaging

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Appropriate use criteria (AUC) are statements that contain indications describing when and how often an intervention should be performed under the optimal combination of scientific evidence, clinical judgment, and patient values while avoiding unnecessary provisions of services. Society of Nuclear Medicine and Molecular Imaging (SNMMI) is a qualified provider-led entity under the Medicare AUC program for advanced diagnostic imaging, allowing referring physicians to use SNMMI AUC to fulfill the requirements of the 2014 Protecting Access to Medicare Act. SNMMI follows a balanced multidisciplinary approach to guidance development by including various stakeholders in the development process. For background and a detailed explanation of this development process, see http://www.snmmi.org/ClinicalPractice/content.aspx?ItemNumber=15665. The full version of this document, including information on methodology, conflicts of interest, benefits and arms, definition of terms list of external reviewers, and additional special commentary, is available at www.snmmi.org/auc. This article is a summary of the complete text of the AUC, which is available at www.snmmi.org/auc.

EXECUTIVE SUMMARY

The value of nuclear medicine imaging for diagnosing infections, was first recognized nearly 50 y ago (*1*). The 3-phase bone scan was for many years the radionuclide test of choice for musculoskeletal infection, with an accuracy exceeding 90% in patients with unviolated bone. Over time, with the advent of new cross-sectional imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI), patients referred for radionuclide imaging increasingly had preexisting conditions. These conditions adversely affect the specificity of bone scintigraphy and necessitated the development of adjunctive and/or alternative procedures, including ^{67}Ga-citrate (^{67}Ga) scintigraphy, labeled leukocyte scintigraphy, and, more recently, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), to facilitate the differentiation of infection from other entities associated with increased bone mineral turnover (*2*).

The document describes the appropriate use of nuclear medicine imaging in patients suspected of having musculoskeletal infections. It is anticipated that, based on the recommendations provided, these imaging tests will be appropriately applied to improve the care of patients. These AUC were developed by an autonomous workgroup of representatives from the SNMMI, the American College of Nuclear Medicine (ACNM), and a hospitalist. These criteria were developed in accordance with the Protecting Access to Medicare Act of 2014, which requires that all referring physicians consult AUC through a clinical decision support mechanism prior to ordering advanced diagnostic imaging tests (*3*). The AUC in this document are intended to assist referring health-care providers in the appropriate use of nuclear medicine imaging in patients suspected of having musculoskeletal infection.

INTRODUCTION

Musculoskeletal infection is a general term that includes osteomyelitis, orthopedic hardware infections (including periprosthetic joint infections [PJIs]), and septic arthritis. These infections can arise hematogenously from a remote location or by direct inoculation, that is, spread of organisms from direct trauma or a contiguous focus of infection and from postoperative sepsis. Local risk factors include open fractures, recent surgery, and orthopedic hardware. Systemic risk factors include diabetes mellitus, immunosuppression, and substance abuse. The diagnosis of musculoskeletal infection is not always obvious, and nuclear medicine imaging is frequently performed as part of the diagnostic workup. No one procedure is equally efficacious for all indications. The selection of an appropriate study is governed by the clinical question(s) posed (*2*).

Much of the nuclear medicine literature has focused on the role of radionuclide imaging for diagnosing pedal osteomyelitis in diabetes, spondylodiscitis, and infections involving orthopedic hardware, including joint prostheses. At one time, the most extensively investigated and widely used radionuclides for musculoskeletal infection were bone, ^{67}Ga, and labeled leukocyte scintigraphy. More recently, ^{18}F-FDG has assumed an increasingly important role in musculoskeletal infection imaging. Consequently, the workgroup chose to focus on the roles of these radiopharmaceuticals for each of these conditions, along with septic arthritis.

There are several limitations to the literature regarding the value of radionuclide imaging in musculoskeletal infection. Published results consist primarily of retrospective investigations, with relatively few subjects, performed at a single institution, and using various standards of truth against which the test is judged. Well-designed prospective multicenter investigations are virtually nonexistent. In the absence of published data, the authors of this document relied on expert opinion from nuclear medicine specialists in the United States, Europe, Africa, and the referring clinical community.

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The workgroup is of the opinion that the most accurate assessment of the utility of nuclear medicine imaging in musculoskeletal infection is obtained by combining existing literature with the opinions of multidisciplinary experts. The recommendations provided relate only to the appropriate use of nuclear medicine imaging and do not preclude other testing, nor are they intended to replace clinical judgment. Referring health-care providers should consider patient history, physical examination, and other test results when contemplating nuclear medicine imaging. This document may also be helpful by providing guidance for imaging specialists, as well as for developers of clinical decision support tools.

METHODOLOGY

The experts of this AUC workgroup were convened by the SNMMI to represent a multidisciplinary panel of health-care providers with substantive knowledge in the use of nuclear medicine procedures in musculoskeletal infection imaging. In addition to SNMMI members, representatives from the ACNM were included in the workgroup. Ten physician members were ultimately selected to participate and contribute to the AUC. A complete list of workgroup participants and external reviewers can be found in Supplemental Appendix A (supplemental materials are available at http://jnm.snmjournals.org).

Supplemental Appendix B presents a summary of definitions of terms and acronyms, Supplemental Appendix C provides disclosures and conflicts-of-interest statements, and Supplemental Appendix D describes the solicitation of public commentary.

AUC Development

The process for AUC development was modeled after the RAND/UCLA Appropriateness Method for AUC development (*4*). It included identifying a list of relevant clinical scenarios where nuclear medicine can be used in the imaging of musculoskeletal infections, a systematic review of evidence related to these clinical scenarios, and a systematic synthesis of available evidence, followed by the development of AUC for each of the various clinical scenarios by using a modified Delphi process. This process strove to adhere to the Institute of Medicine's standards for developing trustworthy clinical guidance (*5*). The final document was drafted on the basis of group ratings and discussions.

Scope and Development of Clinical Scenarios

To begin this process, the workgroup discussed various potential clinical scenarios for the appropriate use of musculoskeletal infection imaging. For clinical scenarios, the relevant populations of interest were children and adults of all genders, ages, races, and geographic locations with known or suspected infections. The specific subgroups of interest were patients who were immunocompetent, who were immunosuppressed (e.g., owing to human immunodeficiency virus [HIV], tumor, transplant), or who had diabetes mellitus; patients who had prosthetic material (hardware, vascular grafts, cardiac implantable devices); and patients who were pregnant.

The workgroup identified 63 clinical scenarios for musculoskeletal infection imaging, which were evaluated and addressed in 8 sections (Section 1: Diagnosis of Spondylodiscitis in Patients Without Spinal Hardware; Section 2: Diagnosis of Spondylodiscitis in Patients with Spinal Hardware; Section 3: Diagnosis of Uncomplicated Peripheral Bone Osteomyelitis; Section 4: Diagnosis of Complicated Peripheral Bone Osteomyelitis, Including Orthopedic Hardware Infection; Section 5: Diagnosis of Foot Osteomyelitis in Diabetic Patients; Section 6: Diagnosis of PJI of the Hip and Knee; Section 7: Diagnosis of PJI of the Shoulder; and Section 8: Diagnosis of Septic Arthritis). The scenarios are intended to be as representative of the relevant patient population as possible for the development of AUC. The resulting AUC are based on evidence and expert opinion regarding diagnostic accuracy and effects on clinical outcomes and clinical decision making as applied to each scenario. Other factors affecting the AUC recommendations were potential harm, including long-term harm that may be difficult to capture; costs; availability; and patient preferences.

Systematic Review

To inform the workgroup, a systematic review of the relevant evidence was commissioned by an independent group, the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (*6*). The primary purpose of the systematic review was to synthesize the evidence on the accuracy of nuclear medicine imaging techniques for the diagnosis of infectious and inflammatory conditions and on the effects of nuclear medicine imaging on clinical outcomes and clinical decision making. The workgroup selected the following key questions to guide the review:

1. What is the accuracy of bone scintigraphy with or without single-photon emission computed tomography (SPECT) or SPECT/CT for the diagnosis of osteomyelitis?
2. What is the accuracy of in vitro labeled leukocyte scintigraphy with or without SPECT or SPECT/CT for the diagnosis of infection?
3. What is the accuracy of in vitro labeled leukocyte scintigraphy with or without SPECT or SPECT/CT for the diagnosis of an inflammatory condition?
4. What is the accuracy of ^{67}Ga scintigraphy with or without SPECT or SPECT/CT for the diagnosis of infection?
5. What is the accuracy of ^{67}Ga scintigraphy with or without SPECT or SPECT/CT for the diagnosis of an inflammatory condition?
6. What is the accuracy of PET, PET/CT, or PET/MRI with ^{18}F-FDG for the diagnosis of an infection?
7. What is the accuracy of PET, PET/CT, or PET/MRI with ^{18}F-FDG for the diagnosis of an inflammatory condition?
8. What are the effects of nuclear medicine imaging testing for suspected infection or an inflammatory condition on clinical outcomes or clinical decision making (e.g., use of treatments, subsequent tests)?

For key questions 1 through 7, the reviewers assessed the effects of the use of alternative tracers, different imaging methods, and demographic and clinical characteristics of the populations (e.g., immunocompetent, immunosuppressed, diabetic, prosthetic materials, pregnant patients) to the extent possible.

The inclusion and exclusion criteria for papers for this review were based on the study parameters established by the workgroup, using the PICOTS (population, intervention, comparisons, outcomes, timing, and setting) approach. Searches for relevant studies and systematic reviews were conducted on the following databases: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE (through January 2018). These searches were supplemented by reviewing the reference lists of relevant publications and suggestions from SNMMI workgroup members.

Two investigators independently reviewed abstracts and full-text articles against prespecified eligibility criteria, as defined by PICOTS. The population comprised patients with suspected

infectious conditions (osteomyelitis, including PJIs and orthopedic hardware infections; spondylodiscitis; bacteremia; infected liver or kidney cysts; cardiovascular infections; AIDS-associated infections; tuberculosis; diabetic foot infections; pneumonia; and abdominal abscess); inflammatory conditions (sarcoidosis, vasculitis, inflammatory bowel disease, and inflammatory arthritis); and Fever of Unknown Origin. The imaging modalities were as follows:

- ^{99m}Tc bone scintigraphy, with or without SPECT or SPECT/CT
- ^{99m}Tc or ^{111}In in vitro labeled leukocyte scintigraphy, with or without SPECT or SPECT/CT
- ^{67}Ga scintigraphy, with or without SPECT or SPECT/CT
  ^{18}F-FDG PET, PET/CT, or PET/MRI

For questions on diagnostic accuracy, the reviewers included cross-sectional and cohort studies and systematic reviews of cross-sectional and cohort studies that reported the diagnostic accuracy of the imaging modality against a reference standard. For osteomyelitis and PJIs, they restricted inclusion to studies that used histopathological findings for osteomyelitis cases and used histopathological findings or clinical follow-up for at least 3 mo as the reference standard. For other infectious conditions and inflammatory conditions, included studies were those that used histopathological or microbiological findings as part of the reference standard, with or without clinical follow-up. Reviewers excluded studies in which the reference standard was unclear or not reported, consisted only of clinical follow-up, or was based on alternative imaging findings only. Primary studies on diagnostic accuracy were also excluded if they used a case-control design or enrolled cases only.

For effects on clinical outcomes, reviewers included cohort studies of nuclear medicine imaging versus no nuclear medicine imaging that reported mortality, morbidity, or other clinical outcomes. For effects on clinical decision making, reviewers included cohort studies and imaging series of nuclear medicine imaging that reported effects on subsequent use of tests and treatments. In lieu of primary studies, when available, reviewers included good- and fair-quality systematic reviews and metaanalyses that were most relevant to the key questions and scope and had more recent search dates. They did not conduct updated metaanalyses to incorporate new studies. Rather, they conducted a qualitative examination of the results of new studies and the degree to which they were consistent or inconsistent with pooled or qualitative findings from prior systematic reviews and metaanalyses. Non-English language articles and studies published only as conference abstracts were excluded.

Two investigators independently assessed the quality (risk of bias) of each study as "good," "fair," or "poor" by using predefined criteria that were specific for each study design. AMSTAR (A MeaSurement Tool to Assess systematic Reviews) (*7*) was used for systematic reviews (except diagnostic accuracy), adapted by the U.S. Preventive Services Task Force criteria for randomized trials and cohort studies, and QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) (*8*) for primary studies and systematic reviews of diagnostic accuracy. Discrepancies were resolved through a consensus process. The strength of the overall evidence was graded as high, moderate, low, or very low using GRADE methods based on quality of evidence, consistency, directness, precision, and reporting bias.

Database searches, review of reference lists, and suggestions from experts resulted in 6,537 potentially relevant articles. After a dual review of abstracts and titles, 1,334 articles were selected for full-text dual review. Of these, 51 studies were determined to meet inclusion criteria and were included in this review. In addition, 24 systematic reviews on diagnostic accuracy, covering a total of 255 unique studies, were also included in this review.

Rating and Scoring

In developing these AUC for musculoskeletal infection imaging, the workgroup members used the following definition of appropriateness to guide their considerations and group discussions: "The concept of appropriateness, as applied to health care, balances risk and benefit of a treatment, test, or procedure in the context of available resources for an individual patient with specific characteristics" (*9*).

At the beginning of the process, workgroup members convened via webinar/teleconference to develop the initial clinical indications. On evaluating the evidence summary of the systematic literature review, the workgroup further refined its draft clinical indications to ensure their accuracy and facilitate consistent interpretation when scoring each indication for appropriateness. Using the evidence summary, workgroup members were first asked individually to assess the appropriateness and provide a score for each of the identified indications. Workgroup members then convened in a group setting for several successive webinars to discuss each indication and associated scores from the first round of individual scoring. After deliberate discussion, a consensus score was determined and then assigned to the associated appropriate use indication. For this scoring round, the expert panel was encouraged to include their clinical expertise in addition to the available evidence in determining the final scores. All members contributed to the final discussion, and no one was forced into consensus. After the rating process was completed, the final appropriate use ratings were summarized in a format similar to that outlined by the RAND/UCLA Appropriateness Method.

The workgroup scored each indication as "appropriate," "may be appropriate," or "rarely appropriate" on a scale from 1 to 9. Scores 7–9 indicate that the use of the procedure is appropriate for the specific clinical indication and is generally considered acceptable. Scores 4–6 indicate that the use of the procedure may be appropriate for the specific indication. This implies that more research is needed to classify the indication definitively. Scores 1–3 indicate that the use of the procedure is rarely appropriate for the specific indication and generally is not considered acceptable.

As stated by other societies that develop AUC, the division of these scores into 3 general levels of appropriateness is partially arbitrary, and the numeric designations should be viewed as a continuum. In addition, if there was a difference in clinical opinion for an indication such that workgroup members could not agree on a common score, that indication was given a "may be appropriate" rating to indicate a lack of agreement on appropriateness based on the available literature and the members' collective clinical opinion, indicating the need for additional research.

SECTION 1: DIAGNOSIS OF SPONDYLODISCITIS IN PATIENTS WITHOUT SPINAL HARDWARE

Introduction

Spondylodiscitis, also known as spinal or vertebral osteomyelitis or septic discitis, is an infection of the vertebral body and/or disc. It accounts for about 1% of all cases of osteomyelitis, with bimodal peaks: below the age of 20 y and from 50 to 70 y. The infection may extend into the epidural space, posterior elements, and paraspinal soft tissues. Preexisting conditions such as

endocarditis, septic arthritis, urinary tract infections, and indwelling catheter infections predispose individuals to these infections. Advanced age, diabetes mellitus, coronary artery disease, spinal interventions, immunosuppression, and intravenous drug use are additional risk factors. The incidence of spondylodiscitis is increasing; this is probably related to aging of the population with a large number of chronic morbidities, increasing use of intravenous medications and drug abuse, and a growing number of spinal surgeries and instrumentation. Spondylodiscitis usually results from hematogenous spread from a remote site of infection. Less frequently, it is due to direct inoculation at the time of surgery or during spinal procedures, or to penetrating trauma. Occasionally, spondylodiscitis can result from contiguous spread of an adjacent soft-tissue infection. The lumbar, thoracic, and cervical spine, in decreasing order of prevalence, are the major sites of involvement. In about 65% of cases, the infection involves a single spinal segment, which includes 2 contiguous vertebral bodies and the intervening disc. Multilevel contiguous infection occurs in about 20% of cases and noncontiguous infection in about 10% of cases (*10*). In developing countries and among HIV-infected patients, *Mycobacterium tuberculosis* is an important cause of spondylodiscitis, affecting the thoracic spine more frequently than the rest of the spine and with a propensity for multilevel involvement (*11*).

Background

Clinical and laboratory evaluations are often not sufficient for diagnosing spondylodiscitis, which is frequently an indolent disease. The interval between the onset of symptoms and diagnosis may be long (*12*). Back pain, which is present in a myriad of other conditions affecting the spine, followed by fever (seen in about 50% of cases) are the most common presenting symptoms. C-reactive protein levels and erythrocyte sedimentation rate are often elevated, but are not specific, and the peripheral white blood cell count is not sensitive (*10*). Imaging, therefore, plays an important role in the diagnosis of spondylodiscitis.

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of spondylodiscitis in patients without spinal hardware, along with final AUC scores, are presented in Table 1.

Scenario 1: Diagnosis of spondylodiscitis in patients without spinal hardware, bone scintigraphy (^{99m}Tc-methylene diphosphate [MDP] or ^{99m}Tc-hydroxyethylene diphosphate [HDP]) (Score 3 – Rarely Appropriate)

No systematic reviews addressed the role of bone scintigraphy for diagnosing spondylodiscitis. The diagnostic performance of bone scintigraphy varies significantly depending on the study technique, such as planar, 3-phase, or SPECT (*13*). In a study that evaluated the diagnostic performance of bone scintigraphy in spondylodiscitis, the reported sensitivity, specificity, and accuracy were 73%, 69%, and 71%, respectively, when bone SPECT was interpreted alone. Inclusion of planar images in scan interpretation improved sensitivity (82%), but with a significant decrease in specificity (23%). Three-phase bone scintigraphy was specific (92%) but not sensitive (36%) (*14*). Although bone scintigraphy is frequently used as a screening test, false-negative results have been reported in elderly patients, possibly secondary to arteriosclerosis-induced ischemia. Furthermore, the test is not sensitive for detecting the soft-tissue infections that may accompany, or mimic, spondylodiscitis (*2*,*10*). For these reasons, it is the expert opinion of the workgroup that, if used at all, bone scintigraphy should not be the sole radionuclide test performed in suspected spondylodiscitis.

Scenario 2: Diagnosis of spondylodiscitis in patients without spinal hardware, ^{67}Ga scintigraphy (Score 5 – May be Appropriate)

No systematic reviews addressed the role of ^{67}Ga scintigraphy for diagnosing spondylodiscitis. The reported sensitivity and specificity of ^{67}Ga scintigraphy for diagnosing spondylodiscitis ranges from 73% to 100% and from 61% to 92%, respectively. Performing SPECT and SPECT/CT improves the diagnostic accuracy. ^{67}Ga scintigraphy is more sensitive than bone scintigraphy for detecting soft-tissue infections that accompany or mimic spondylodiscitis and may be more sensitive than bone scintigraphy in elderly patients. The 24- to 48-h delay between radiopharmaceutical administration and imaging and the relatively poor image quality, however, are disadvantages of this agent (*10*). ^{67}Ga is less accurate than ^{18}F-FDG PET and PET/CT for diagnosing spondylodiscitis and for identifying paraspinal soft-tissue infections that often accompany spondylodiscitis (*15*,*16*).

Scenario 3: Diagnosis of spondylodiscitis in patients without spinal hardware, combined bone/^{67}Ga scintigraphy (Score 6 – May be Appropriate)

No systematic reviews addressed the role of combined bone/^{67}Ga scintigraphy for diagnosing spondylodiscitis. Available data suggest that the accuracy of combined bone/^{67}Ga scintigraphy, both planar and SPECT, is similar to that of ^{67}Ga scintigraphy alone (*14*). In a comparison of combined bone/^{67}Ga

TABLE 1
Clinical Scenarios for the Diagnosis of Spondylodiscitis in Patients Without Spinal Hardware

Scenario no.	Description	Appropriateness	Score
1	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	Rarely appropriate	3
2	^{67}Ga scintigraphy	May be appropriate	5
3	Combined bone/^{67}Ga scintigraphy	May be appropriate	6
4	Labeled leukocyte scintigraphy	Rarely appropriate	2
5	Combined labeled leukocyte/bone scintigraphy	Rarely appropriate	2
6	Combined labeled leukocyte/bone marrow scintigraphy	Rarely appropriate	2
7	^{18}F-FDG PET and PET/CT	Appropriate	9

scintigraphy with ^{18}F-FDG PET/CT, the accuracy was 79% versus 88%, respectively. Results of bone scintigraphy and ^{67}Ga scintigraphy individually, however, were not provided (*16*). A recent investigation that used combined bone/^{67}Ga SPECT/CT reported an accuracy of 97% for diagnosing spondylodiscitis, similar to the results reported for ^{18}F-FDG PET and PET/CT (*17*). Nevertheless, the combined study requires 2 different tracers, as well as multiple, sometimes lengthy, imaging sessions on different days.

Scenario 4: Diagnosis of spondylodiscitis in patients without spinal hardware, labeled leukocyte scintigraphy (Score 2 – Rarely Appropriate)

The role of labeled leukocyte scintigraphy for diagnosing osteomyelitis of the spine was addressed in one systematic review, in which the quality of evidence was fair (*18*). The sensitivity and specificity of labeled leukocyte imaging for diagnosing osteomyelitis in the central skeleton, including the spine, were reported to be 21% and 60%, respectively. A major limitation of labeled leukocyte scintigraphy is that 50% or more of the cases of spondylodiscitis, for reasons that are not well understood, present as nonspecific areas of decreased or absent activity (*19*). In an investigation of 71 patients with suspected spondylodiscitis, the accuracy of labeled leukocyte scintigraphy (66%) was similar to that of bone scintigraphy (63%) (*19*).

Scenario 5: Diagnosis of spondylodiscitis in patients without spinal hardware, combined labeled leukocyte/bone scintigraphy (Score 2 – Rarely Appropriate)

There were no data on combined labeled leukocyte/bone scintigraphy for diagnosing spondylodiscitis in the systematic reviews. Because of its high sensitivity, bone scintigraphy is often used as a screening test for osteomyelitis. When the results are positive for osteomyelitis, labeled leukocyte imaging is performed to improve specificity. In the case of spondylodiscitis, many of the noninfectious conditions associated with increased activity on bone scintigraphy are also associated with nonspecific decreased uptake on labeled leukocyte imaging (*19*). Consequently, it is the expert opinion of the workgroup that combined labeled leukocyte/bone scintigraphy is not likely to improve the specificity of bone scintigraphy and should not be used for diagnosing spondylodiscitis.

Scenario 6: Diagnosis of spondylodiscitis in patients without spinal hardware, combined labeled leukocyte/bone marrow scintigraphy (Score 2 – Rarely Appropriate)

There were no data on combined labeled leukocyte/bone marrow scintigraphy for diagnosing spondylodiscitis in the systematic reviews. Bone marrow scintigraphy facilitates the differentiation of labeled leukocyte accumulation in infection from accumulation in bone marrow (*2*). A prerequisite for performing bone marrow imaging is the presence of labeled leukocyte accumulation in the area of concern. Since 50% or more of all spondylodiscitis cases present as decreased or absent activity on labeled leukocyte imaging, it is the expert opinion of the workgroup that combined labeled leukocyte/bone marrow scintigraphy would not be helpful and should not be performed for diagnosing spondylodiscitis.

Scenario 7: Diagnosis of spondylodiscitis in patients without spinal hardware, ^{18}F-FDG PET and PET/CT (Score 9 – Appropriate)

One systematic review addressed the role of *^{18}F-FDG PET and PET/CT* for diagnosing spondylodiscitis. The quality of the evidence was fair. The pooled sensitivity and specificity were 97% and 88%, respectively, with positive and negative likelihood ratios of 8.19 and 0.03, respectively (*20*). In a more recent metaanalysis, ^{18}F-FDG PET/CT demonstrated a pooled sensitivity of 94.8% (95% confidence interval [CI], 88.9%–97.6%) and a pooled specificity of 91.4% (95% CI, 78.2%–96.9%). The pooled positive and negative likelihood ratios were 4.7 (95% CI, 2.9–7.7) and 0.11 (95% CI, 0.07–0.16), respectively (*21*). Published data indicate that ^{18}F-FDG PET and PET/CT are more accurate than ^{67}Ga for diagnosing spondylodiscitis and for identifying accompanying paraspinal soft-tissue infections (*15*,*16*).

SUMMARY OF RECOMMENDATIONS

^{18}F-FDG PET and PET/CT are the nuclear medicine imaging tests of choice for diagnosing spondylodiscitis. When ^{18}F-FDG PET and PET/CT cannot be performed, ^{67}Ga scintigraphy alone or in combination with bone scintigraphy, preferably with SPECT or SPECT/CT, is an acceptable alternative. Because of poor sensitivity for the paravertebral soft-tissue infections that may accompany spondylodiscitis, bone scintigraphy should not be performed alone but could be performed in conjunction with ^{67}Ga scintigraphy. There is no role for labeled leukocyte scintigraphy, alone or in combination with bone or bone marrow scintigraphy, for diagnosing spondylodiscitis.

SECTION 2: DIAGNOSIS OF SPONDYLODISCITIS IN PATIENTS WITH SPINAL HARDWARE

Introduction

Postoperative spondylodiscitis has a prevalence ranging from 0.5% to approximately 19%, depending on comorbidities, surgical technique, and hardware used. The presentation of postoperative spondylodiscitis is often indolent and nonspecific. Although superficial infections are easily diagnosed, diagnosis of deeper infections is more challenging. Fever is present in only about half of the cases and laboratory tests are of limited value. The most common presentation is that of nonspecific back pain and constitutional symptoms. Prompt diagnosis is imperative because a delay may lead to spread of infection to the bone, epidural space, and paravertebral soft tissues, with formation of biofilm around the hardware. Biofilm is an impediment to successful antibiotic treatment and may necessitate hardware removal, which can lead to instability and pseudoarthrosis (*22*).

Background

Because the diagnosis of postoperative spondylodiscitis is not always obvious, imaging studies play an integral role in the workup of a symptomatic individual. Cross-sectional imaging studies such as CT and MRI are hampered by hardware-induced artifacts, even when metallic artifact reduction software is used. Nuclear medicine imaging tests are less affected by the presence of hardware and are valuable in the workup of postoperative spondylodiscitis (*10*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of spondylodiscitis in patients with spinal hardware, along with final AUC scores, are presented in Table 2.

Scenario 8: Diagnosis of spondylodiscitis in patients with spinal hardware, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 3 – Rarely Appropriate)

TABLE 2
Clinical Scenarios for the Diagnosis of Spondylodiscitis in Patients with Spinal Hardware

Scenario no.	Description	Appropriateness	Score
8	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	Rarely appropriate	3
9	^{67}Ga scintigraphy	May be appropriate	5
10	Combined bone/^{67}Ga scintigraphy	May be appropriate	6
11	Labeled leukocyte scintigraphy	Rarely appropriate	2
12	Combined labeled leukocyte/bone scintigraphy	Rarely appropriate	2
13	Combined labeled leukocyte/bone marrow scintigraphy	Rarely appropriate	2
14	^{18}F-FDG PET and PET/CT	Appropriate	8

There were no data in the systematic reviews on the role of bone scintigraphy for diagnosing spondylodiscitis in patients with spinal hardware. It is well known that preexisting conditions such as orthopedic hardware adversely affect the specificity of bone scintigraphy in general. As already noted, false-negative results have been reported in elderly patients, and the test is not sensitive for detecting paravertebral soft-tissue infections that may accompany or mimic spondylodiscitis (*2*,*10*). For these reasons, it is the expert opinion of the workgroup that, if used at all, bone scintigraphy should not be the sole radionuclide test performed in patients with spinal hardware with suspected spondylodiscitis.

Scenario 9: Diagnosis of spondylodiscitis in patients with spinal hardware, ^{67}Ga scintigraphy (Score 5 – May be Appropriate)

There were no data in the systematic reviews and only limited data overall on the role of ^{67}Ga scintigraphy for diagnosing spondylodiscitis in patients with spinal hardware. In one investigation, ^{67}Ga scintigraphy could not differentiate postoperative changes from infection (*23*). ^{18}F-FDG PET and PET/CT are superior to combined bone/^{67}Ga scintigraphy for diagnosing spondylodiscitis in general (*15*,*16*). Therefore, it is the expert opinion of the workgroup that ^{67}Ga scintigraphy should be used for diagnosing spondylodiscitis in patients with spinal hardware only when ^{18}F-FDG PET and PET/CT are not available.

Scenario 10: Diagnosis of spondylodiscitis in patients with spinal hardware, combined bone/^{67}Ga scintigraphy (Score 6 – May be Appropriate)

In the systematic reviews, there were no data on the role of combined bone/^{67}Ga scintigraphy for diagnosing spondylodiscitis in patients with spinal hardware. ^{18}F-FDG PET and PET/CT are superior to combined bone/^{67}Ga scintigraphy for diagnosing spondylodiscitis in general (*15*,*16*). Therefore, it is the expert opinion of the workgroup that combined bone/^{67}Ga scintigraphy should be used for diagnosing spondylodiscitis in patients with spinal hardware only when ^{18}F-FDG PET and PET/CT are not available.

Scenario 11: Diagnosis of spondylodiscitis in patients with spinal hardware, labeled leukocyte scintigraphy (Score 2 – Rarely Appropriate)

In the systematic reviews, there were no data on the role of labeled leukocyte scintigraphy for diagnosing spondylodiscitis in patients with spinal hardware. In one systematic review, in which the quality of evidence was fair, the sensitivity and specificity of labeled leukocyte imaging for diagnosing osteomyelitis in the central skeleton, including the spine, were reported to be 21% and 60%, respectively (*18*). Given the poor performance of labeled leukocyte scintigraphy for diagnosing spondylodiscitis in general, it is the expert opinion of the workgroup that this test should not be used for diagnosing spondylodiscitis in patients with spinal hardware.

Scenario 12: Diagnosis of spondylodiscitis in patients with spinal hardware, combined labeled leukocyte/bone scintigraphy (Score 2 – Rarely Appropriate)

There are no systematic reviews on the role of combined labeled leukocyte/bone scintigraphy for diagnosing spondylodiscitis in patients with spinal hardware. Labeled leukocyte imaging is often performed to improve the specificity of bone scintigraphy. In the case of spondylodiscitis, many conditions that result in a false-positive result on bone scintigraphy appear as decreased uptake on labeled leukocyte imaging (*19*). Consequently, it is the expert opinion of the workgroup that performing labeled leukocyte together with bone scintigraphy is not likely to improve the specificity of bone scintigraphy for diagnosing spondylodiscitis, and therefore combined labeled leukocyte/bone scintigraphy should not be used for diagnosing spondylodiscitis in patients with spinal hardware.

Scenario 13: Diagnosis of spondylodiscitis in patients with spinal hardware, combined labeled leukocyte/bone marrow scintigraphy (Score 2 – Rarely Appropriate)

There were no systematic reviews on the role of combined labeled leukocyte/bone marrow scintigraphy for diagnosing spondylodiscitis in patients with spinal hardware. Bone marrow scintigraphy facilitates the differentiation of labeled leukocyte accumulation in osteomyelitis from accumulation in bone marrow (*2*). It is the expert opinion of the workgroup that because 50% or more of spondylodiscitis cases present as areas of decreased or absent activity on labeled leukocyte imaging, performing complementary bone marrow scintigraphy in these cases would not improve the specificity of the test. Therefore, combined labeled leukocyte/bone marrow scintigraphy should not be used for diagnosing spondylodiscitis in patients with spinal hardware.

Scenario 14: Diagnosis of spondylodiscitis in patients with spinal hardware, ^{18}F-FDG PET and PET/CT (Score 8 – Appropriate)

One systematic review included data on ^{18}F-FDG PET and PET/CT for diagnosing spondylodiscitis in patients with spinal hardware (*20*). The quality of the evidence was fair. The summary

TABLE 3
Clinical Scenarios for the Diagnosis of Uncomplicated Peripheral Bone Osteomyelitis

Scenario no.	Description	Appropriateness	Score
15	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	Appropriate	7
16	^{67}Ga scintigraphy	Rarely appropriate	2
17	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	2
18	Labeled leukocyte scintigraphy	May be appropriate	6
19	Combined labeled leukocyte/bone scintigraphy	May be appropriate	6
20	Combined labeled leukocyte/bone marrow scintigraphy	May be appropriate	6
21	^{18}F-FDG PET and PET/CT	Appropriate	9

AUC for spondylodiscitis was 0.98 versus 0.92 in patients with spinal hardware. False-positive results were more common in patients with spinal hardware than they were in patients without it (12.8% vs. 7%), presumably due to hardware-induced aseptic inflammation. Performing PET/CT rather than PET alone appears to reduce hardware-associated false-positive results (*10*). Although there are no comparative investigations of ^{18}F-FDG PET and PET/CT with bone, ^{67}Ga scintigraphy, or labeled leukocyte scintigraphy in patients with spinal hardware, ^{18}F-FDG PET and PET/CT have outperformed these tests for diagnosing spondylodiscitis in general (*15*,*16*,*18*). Therefore, it is the expert opinion of the workgroup that ^{18}F-FDG PET and PET/CT are the most appropriate radionuclide imaging tests for diagnosing spondylodiscitis in patients with spinal hardware.

SUMMARY OF RECOMMENDATIONS

^{18}F-FDG PET and PET/CT are the nuclear medicine imaging tests of choice for spondylodiscitis in patients with spinal hardware. ^{67}Ga scintigraphy alone or in combination with bone scintigraphy should be used only when ^{18}F-FDG PET and PET/CT are not available. Because of poor sensitivity for the paravertebral soft-tissue infections that may accompany spondylodiscitis, bone scintigraphy should not be performed alone but could be performed in conjunction with ^{67}Ga scintigraphy. Labeled leukocyte scintigraphy alone or in combination with bone or bone marrow scintigraphy should not be used to diagnose spondylodiscitis in patients with spinal hardware.

DIAGNOSIS OF UNCOMPLICATED PERIPHERAL BONE OSTEOMYELITIS

Introduction

Osteomyelitis, an infectious process of the bone caused by bacteria, viruses, and fungi, can arise either hematogenously or via direct or contiguous inoculation. Hematogenous osteomyelitis is caused by seeding of organisms that are transported by the blood from a remote source to the bone. It occurs most often in children. Direct or contiguous inoculation osteomyelitis is caused by the spread of organisms from direct trauma, a contiguous focus of infection, or sepsis following surgery. Predisposing conditions include diabetes mellitus, sickle cell disease, intravenous drug abuse, alcoholism, and immunosuppression, as well as open fractures, recent orthopedic surgery, and joint prostheses (*24*).

Background

The diagnosis of osteomyelitis is not always obvious. Signs and symptoms are often nonspecific and the diagnosis cannot be made on the basis of laboratory tests alone. Consequently, imaging procedures are performed routinely as part of the diagnostic workup. Although plain radiography is usually the initial imaging study performed, radionuclide imaging is frequently incorporated into the diagnostic workup of osteomyelitis (*24*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the use of nuclear medicine in the diagnosis of uncomplicated peripheral bone osteomyelitis, along with final AUC scores, are presented in Table 3.

Scenario 15: Diagnosis of uncomplicated peripheral bone osteomyelitis, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 7 – Appropriate)

No systematic reviews specifically addressed bone scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis. In a review of several studies totaling 574 patients, the sensitivity and specificity of 3-phase bone scintigraphy were 94% and 95%, respectively (*25*).

Scenario 16: Diagnosis of uncomplicated peripheral bone osteomyelitis, ^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews specifically addressed ^{67}Ga scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis. There was one systematic review on the accuracy of ^{67}Ga scintigraphy for the diagnosis of chronic osteomyelitis (n = 92), defined as osteomyelitis requiring more than one episode of treatment and/or persistent infection lasting more than 6 wk. None of the studies included in the review evaluated ^{67}Ga scintigraphy with SPECT or SPECT/CT. The level of evidence was fair. The pooled sensitivity of the test was 0.56 (95% CI, 0.26–0.82) and the pooled specificity was 0.76 (95% CI, 0.49–0.91) (*18*). It is the expert opinion of the workgroup that based on these results together with the availability of labeled leukocyte imaging and ^{18}F-FDG PET/CT that ^{67}Ga scintigraphy does not have a role in diagnosing uncomplicated peripheral bone osteomyelitis.

Scenario 17: Diagnosis of uncomplicated peripheral bone osteomyelitis, combined bone/^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews specifically addressed combined bone/^{67}Ga scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis. Combined bone/^{67}Ga scintigraphy is typically performed to improve the diagnostic specificity of bone scintigraphy in patients with underlying bone abnormalities (*26*). As already noted, the specificity of 3-phase bone scintigraphy for

diagnosing uncomplicated peripheral bone osteomyelitis exceeds 90% (*25*). It is the expert opinion of the workgroup that when imaging in addition to bone scintigraphy is necessary, labeled leukocyte scintigraphy or ^{18}F-FDG PET/CT can be performed. The additional radiation, time, and expense involved does not justify performing combined bone/^{67}Ga scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis.

Scenario 18: Diagnosis of uncomplicated peripheral bone osteomyelitis, labeled leukocyte scintigraphy (Score 6 – May be Appropriate)

No systematic reviews specifically addressed the role of labeled leukocyte scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis. Two systematic reviews addressed the role of labeled leukocyte scintigraphy for diagnosing osteomyelitis in general. The level of evidence in both was fair. In one review, the test had a pooled sensitivity of 0.74 (95% CI, 0.64–0.83) and a pooled specificity of 0.88 (95% CI, 0.80–0.94) for a positive likelihood ratio of 4.71 (95% CI, 1.46–15.16) and a negative likelihood ratio of 0.26 (95% CI, 0.08–0.81) (*27*). There was no statistically significant difference in accuracy between studies performed with ^{111}In-labeled leukocytes or with ^{99m}Tc-labeled leukocytes. The area under the summary receiver operating characteristics curve was 0.91 (SD 0.07) (*27*). In the second review, the pooled sensitivity was 0.61 (95% CI, 0.43–0.76) and the pooled specificity was 0.77 (95% CI, 0.63–0.87) (*18*).

The sensitivity and specificity of 3-phase bone scintigraphy for diagnosing uncomplicated osteomyelitis exceed 90%. It is the expert opinion of the workgroup that the use of labeled leukocyte scintigraphy should be reserved for situations in which the results of bone scintigraphy are inconclusive.

Scenario 19: Diagnosis of uncomplicated peripheral bone osteomyelitis, combined labeled leukocyte/bone scintigraphy (Score 6 – May be Appropriate)

No systematic reviews specifically addressed the role of combined labeled leukocyte/bone scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis. One systematic review addressed the role of combined labeled leukocyte/bone scintigraphy for diagnosing peripheral bone osteomyelitis in general. The level of evidence was fair. The systematic review found that the combined test was more accurate than labeled leukocyte scintigraphy alone, with a pooled sensitivity of 0.78 (95% CI, 0.72–0.83) and a pooled specificity of 0.84 (95% CI, 0.75–0.90) (*18*). Since the sensitivity and specificity of 3-phase bone scintigraphy for diagnosing uncomplicated osteomyelitis exceed 90%, it is the expert opinion of the workgroup that the use of combined labeled leukocyte/bone scintigraphy should be reserved for situations in which the results of bone scintigraphy are inconclusive.

Scenario 20: Diagnosis of uncomplicated peripheral bone osteomyelitis, combined labeled leukocyte/bone marrow scintigraphy (Score 6 – May be Appropriate)

No systematic reviews specifically addressed the role of combined labeled leukocyte/bone marrow scintigraphy for diagnosing uncomplicated peripheral bone osteomyelitis. The accuracy of combined leukocyte/bone marrow scintigraphy for diagnosing osteomyelitis is about 90%, similar to that of 3-phase bone scintigraphy (*2*). It is the expert opinion of the workgroup that combined labeled leukocyte/bone marrow scintigraphy should be reserved for those situations in which the results of bone scintigraphy are inconclusive.

Scenario 21: Diagnosis of uncomplicated peripheral bone osteomyelitis, ^{18}F-FDG PET and PET/CT (Score 9 – Appropriate)

No systematic reviews specifically addressed the role of ^{18}F-FDG PET are PET/CT for diagnosing uncomplicated peripheral bone osteomyelitis. Two systematic reviews addressed the role of ^{18}F-FDG PET and PET/CT for diagnosing osteomyelitis in general. The level of evidence was fair for both. In one systematic review, ^{18}F-FDG PET had a pooled sensitivity of 0.92 (95% CI, 0.87–0.96) and a pooled specificity of 0.92 (95% CI, 0.87–0.96) for the diagnosis of osteomyelitis, for a positive likelihood ratio of 9.77 (95% CI, 5.99–15.95) and a negative likelihood ratio of 0.12 (95% CI, 0.07–0.20). The area under the summary receiver operating characteristics curve was 0.97 (*27*). In the second systematic review, ^{18}F-FDG PET had a pooled sensitivity of 0.96 (95% CI, 0.88–0.99) and a pooled specificity of 0.91 (95% CI, 0.81–0.95). ^{18}F-FDG PET was significantly more accurate than labeled leukocyte scintigraphy ($P = 0.03$), bone scintigraphy ($P = 0.0001$), and MRI ($P = 0.001$) (*18*).

SUMMARY OF RECOMMENDATIONS

^{18}F-FDG PET and PET/CT are the nuclear medicine imaging tests of choice for the diagnosis of uncomplicated peripheral bone osteomyelitis. Depending on availability, bone scintigraphy is an acceptable alternative. Labeled leukocyte imaging alone or in combination with bone or bone marrow scintigraphy should be reserved for those circumstances in which ^{18}F-FDG PET and PET/CT or bone scintigraphy are not available or are not diagnostic. ^{67}Ga scintigraphy, alone or in combination with bone scintigraphy, should not be used to diagnose uncomplicated peripheral bone osteomyelitis.

DIAGNOSIS OF COMPLICATED PERIPHERAL BONE OSTEOMYELITIS, INCLUDING ORTHOPEDIC HARDWARE INFECTION

Introduction

The term *complicated osteomyelitis* is used to describe those situations in which infection develops in bone that has been previously violated by processes such as tumors, fractures, and orthopedic hardware. Posttraumatic and postsurgical osteomyelitis can be especially difficult to diagnose. In the early postoperative period, symptoms of infection, such as pain, swelling, and erythema, can also be features of normal fracture healing. Later on, clinical presentations such as persistent pain can be due to both infectious and noninfectious causes. Bone and soft-tissue healing after surgery and trauma may affect image quality and mimic infection.

Background

Nuclear medicine imaging tests reflect functional rather than structural changes and are particularly well suited for diagnosing complicated osteomyelitis.

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, along with final AUC scores, are presented in Table 4.

TABLE 4
Clinical Scenarios for the Diagnosis of Complicated Peripheral Bone Osteomyelitis, Including Orthopedic Hardware Infection

Scenario no.	Description	Appropriateness	Score
22	Bone scintigraphy	Rarely appropriate	3
23	^{67}Ga scintigraphy	Rarely appropriate	3
24	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	3
25	Labeled leukocyte scintigraphy	May be appropriate	5
26	Combined labeled leukocyte/bone scintigraphy	May be appropriate	5
27	Combined labeled leukocyte/bone marrow scintigraphy	Appropriate	8
28	^{18}F-FDG PET and PET/CT	Appropriate	8

Scenario 22: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 3 – Rarely Appropriate)

One systematic review included bone scintigraphy for diagnosing complicated peripheral bone osteomyelitis. The level of evidence was fair. Bone scintigraphy was significantly more sensitive than labeled leukocyte scintigraphy but significantly less sensitive than ^{18}F-FDG PET and PET/CT. The sensitivity was not significantly different from that of combined bone/^{67}Ga scintigraphy and combined bone/labeled leukocyte scintigraphy. Bone scintigraphy was significantly less specific than combined bone/^{67}Ga scintigraphy, labeled leukocyte scintigraphy, combined bone/labeled leukocyte scintigraphy, and ^{18}F-FDG PET and PET/CT (*18*).

Scenario 23: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, ^{67}Ga scintigraphy (Score 3 – Rarely Appropriate)

One systematic review addressed the use of ^{67}Ga scintigraphy for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection. The level of evidence was fair. The pooled sensitivity was 0.56 (95% CI, 0.26–0.82) and the pooled specificity was 0.76 (95% CI, 0.49–0.91) (*18*).

Scenario 24: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, combined bone/^{67}Ga scintigraphy (Score 3 – Rarely Appropriate)

One systematic review addressed combined bone/^{67}Ga scintigraphy for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection. The level of evidence was fair. The combined test was as sensitive as, and significantly more specific than, bone scintigraphy alone. The sensitivity and specificity of combined bone/^{67}Ga scintigraphy did not differ significantly from those of labeled leukocyte scintigraphy and combined labeled leukocyte/bone scintigraphy. The test was as specific as, but significantly less sensitive than, ^{18}F-FDG PET (*18*).

Scenario 25: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, labeled leukocyte scintigraphy (Score 5 – May be Appropriate)

One systematic review addressed labeled leukocyte scintigraphy for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection (*18*). The level of evidence was fair. The pooled sensitivity of labeled leukocyte scintigraphy was not significantly different from that of bone scintigraphy, combined bone/^{67}Ga scintigraphy, and combined labeled leukocyte/bone scintigraphy, but was significantly lower than that of ^{18}F-FDG PET. The specificity of labeled leukocyte scintigraphy was not significantly different from that of combined bone/^{67}Ga scintigraphy or combined labeled leukocyte/bone scintigraphy. The specificity was significantly higher than that of bone scintigraphy but was significantly lower than that of ^{18}F-FDG PET.

Scenario 26: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, combined labeled leukocyte/bone scintigraphy (Score 5 – May be Appropriate)

One systematic review addressed combined labeled leukocyte/bone scintigraphy for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection. The level of evidence was fair (*18*). The sensitivity of combined bone/labeled leukocyte scintigraphy was not significantly different from that of labeled leukocyte scintigraphy alone, bone scintigraphy alone, and combined bone/^{67}Ga scintigraphy. The test was significantly more specific than bone scintigraphy, but not significantly more specific than labeled leukocyte scintigraphy or combined bone/^{67}Ga scintigraphy. Combined bone/labeled leukocyte scintigraphy was significantly less sensitive and specific than ^{18}F-FDG PET.

Scenario 27: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, combined labeled leukocyte/bone marrow scintigraphy (Score 8 – Appropriate)

No systematic reviews addressed combined labeled leukocyte/bone marrow scintigraphy for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection. In one investigation the sensitivity, specificity, and accuracy of combined labeled leukocyte/bone marrow scintigraphy were 100%, 94%, and 96%, respectively (*28*). In another investigation that used computerized bone marrow subtraction, the sensitivity, specificity, and accuracy of combined labeled leukocyte/bone marrow scintigraphy were 95%, 93%, and 94%, respectively (*29*).

Scenario 28: Diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, ^{18}F-FDG PET and PET/CT (Score 8 – Appropriate)

One systematic review addressed ^{18}F-FDG PET for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection (*18*). The level of evidence was fair. ^{18}F-FDG PET was significantly more sensitive than bone, combined

bone/^{67}Ga, labeled leukocyte, and combined labeled leukocyte/bone scintigraphy. It was significantly more specific than bone and leukocyte scintigraphy, but not significantly more specific than combined bone/^{67}Ga and combined labeled leukocyte/bone scintigraphy.

SUMMARY OF RECOMMENDATIONS

For the diagnosis of complicated peripheral bone osteomyelitis, including orthopedic hardware infection, ^{18}F-FDG PET and PET/CT and combined labeled leukocyte/bone marrow scintigraphy are the most appropriate nuclear medicine procedures. Labeled leukocyte scintigraphy alone or in combination with bone scintigraphy can also be used. ^{67}Ga scintigraphy, alone or in combination with bone scintigraphy, does not offer any advantages over any of the other techniques. In view of the delay between injection of ^{67}Ga and imaging, usually 48 h, and the suboptimal imaging characteristics of this radiopharmaceutical, ^{67}Ga scintigraphy and combined bone/gallium scintigraphy should not be used for diagnosing complicated peripheral bone osteomyelitis, including orthopedic hardware infection.

DIAGNOSIS OF FOOT OSTEOMYELITIS IN DIABETIC PATIENTS

Introduction

Diabetic foot infections are defined as infections of the soft tissues or bone below the malleoli in diabetic individuals that usually occur at sites of skin trauma or ulceration. It is estimated that as of 2014 there were more than 422 million adults with diabetes worldwide. The incidence of foot ulcers in this population is about 2%–7% per year. Sixty percent of these ulcers become infected during treatment, and about 20% progress to frank osteomyelitis. Diabetic foot ulcerations are one of the most common reasons for hospitalizations and are associated with increased risk of multiple hospitalizations and amputation. Two thirds of diabetic patients who have foot infections severe enough to require hospitalization have underlying osteomyelitis. These patients have worse outcomes, more surgeries and amputations, longer hospitalizations, and higher rates of recurrent infection and readmission for infection than do patients with soft-tissue infection alone. The importance of a prompt, accurate diagnosis and the institution of appropriate treatment cannot be overemphasized (*30*,*31*).

Background

Diagnosing osteomyelitis underlying a diabetic foot ulcer is challenging because there is no single noninvasive test that is both sensitive and specific. Diabetic patients can have a significant foot infection but lack pain and not mount a systemic inflammatory response, and the diagnosis is often overlooked. Laboratory tests are variable and often nonspecific. Further complicating matters is the neuropathic, or Charcot, joint. Although infection is a relatively uncommon complication of the neuropathic joint, differentiating between the two, or diagnosing infection superimposed on the neuropathic joint, can be difficult (*31*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of foot osteomyelitis in diabetic patients, along with final AUC scores, are presented in Table 5.

Scenario 29: Diagnosis of foot osteomyelitis in diabetic patients, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 2 – Rarely Appropriate)

One systematic review focused on the accuracy of bone scintigraphy for the diagnosis of diabetic foot osteomyelitis (*32*). The level of evidence was fair. None of the studies included SPECT or SPECT/CT. The review found a pooled sensitivity of 0.81 (95% CI, 0.73–0.87) and a pooled specificity of 0.28 (95% CI, 0.17–0.42). In comparison, in the same review, the pooled sensitivity of ^{111}In-labeled leukocyte scintigraphy was 0.74 (95% CI, 0.67–0.80) and the pooled specificity was 0.68 (95% CI, 0.57–0.78).

Scenario 30: Diagnosis of foot osteomyelitis in diabetic patients, ^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews addressed the role of ^{67}Ga scintigraphy for the diagnosis of diabetic foot osteomyelitis. In an investigation of 22 diabetic patients, the sensitivity, specificity, and accuracy of planar imaging were 100%, 40%, and 73%, respectively. ^{67}Ga scintigraphy was more accurate than 3-phase bone scintigraphy (59%), but less accurate than ^{111}In-labeled leukocyte scintigraphy (86%) and combined bone/labeled leukocyte scintigraphy (91%) (*33*). In another investigation the sensitivity and specificity of ^{67}Ga SPECT/CT for diagnosing diabetic foot osteomyelitis were 100% and 45%, respectively (*34*).

Scenario 31: Diagnosis of foot osteomyelitis in diabetic patients, combined bone/^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews addressed the role of combined bone/^{67}Ga scintigraphy for the diagnosis of diabetic foot osteomyelitis. In one investigation of 22 diabetic patients, the sensitivity, specificity, and accuracy of planar combined bone/^{67}Ga scintigraphy were 100%, 40%, and 73%, respectively, identical to that of

TABLE 5
Clinical Scenarios for the Diagnosis of Foot Osteomyelitis in Diabetic Patients

Scenario no.	Description	Appropriateness	Score
29	Bone scintigraphy	Rarely appropriate	2
30	^{67}Ga scintigraphy	Rarely appropriate	2
31	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	2
32	Labeled leukocyte scintigraphy	Appropriate	8
33	Combined labeled leukocyte/bone scintigraphy	Appropriate	8
34	Combined labeled leukocyte/bone marrow scintigraphy	Appropriate	8
35	^{18}F-FDG PET and PET/CT	Appropriate	8

^{67}Ga scintigraphy alone. Combined bone/^{67}Ga scintigraphy, however, was less accurate than ^{111}In-labeled leukocyte scintigraphy (86%) and combined bone/labeled leukocyte scintigraphy (91%) (*33*). In another investigation ($n = 31$), the sensitivity and specificity of combined bone/^{67}Ga scintigraphy were 44% and 77%, respectively (*35*).

Scenario 32: Diagnosis of foot osteomyelitis in diabetic patients, labeled leukocyte scintigraphy (Score 8 – Appropriate)

Two systematic reviews addressed the role of labeled leukocyte scintigraphy for the diagnosis of diabetic foot osteomyelitis. The level of evidence was fair for both. One systematic review included 6 studies, all of which were performed with ^{111}In-labeled leukocytes. None of the studies evaluated SPECT or SPECT/CT. The test had a pooled sensitivity of 0.74 (95% CI, 0.67–0.80) and a pooled specificity of 0.68 (95% CI, 0.57–0.78) for diagnosing diabetic foot osteomyelitis (*32*).

In the second systematic review, the pooled sensitivity of ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO)–labeled leukocyte scintigraphy (91%) was similar to that of ^{111}In-labeled leukocyte scintigraphy (92%), but the pooled specificity was higher (92% vs. 75%). Four studies performed with ^{99m}Tc-HMPAO–labeled leukocytes evaluated scintigraphy with SPECT or SPECT/CT. In these studies, the sensitivity ranged from 0.88 to 1.00 and the specificity from 0.35 to 1.00 (*36*). In an investigation of 213 ^{111}In-labeled leukocyte SPECT/CT studies, the sensitivity was 87% and the specificity was 68% (*37*).

Scenario 33: Diagnosis of foot osteomyelitis in diabetic patients, combined labeled leukocyte/bone scintigraphy (Score 8 – Appropriate)

Combined labeled leukocyte/bone imaging was not addressed in the systematic reviews. In a prospective investigation that used ^{111}In-labeled leukocytes, the sensitivity, specificity, and accuracy of combined bone/labeled leukocyte scintigraphy were 100%, 80%, and 91%, respectively. The combined test was more accurate than 3-phase bone scintigraphy (59%), ^{67}Ga scintigraphy (73%), combined bone/^{67}Ga scintigraphy (73%), and labeled leukocyte scintigraphy (86%) (*33*).

In a prospective investigation that used ^{99m}Tc-labeled leukocytes without SPECT or SPECT/CT, the sensitivity of combined labeled leukocyte/bone scintigraphy was 88% (23/26) and the specificity was 97% (29/30). The results of the combined test were not compared with labeled leukocyte scintigraphy alone (*38*).

In another prospective investigation that used ^{99m}Tc-labeled leukocytes, the sensitivity of combined labeled leukocyte/bone scintigraphy was 93% (38/41) and the specificity was 98% (41/42). The results of the combined study were not compared with labeled leukocyte imaging alone (*39*).

One retrospective investigation that used ^{111}In-labeled leukocytes evaluated combined bone/labeled leukocyte SPECT/CT for diagnosing diabetic foot osteomyelitis. The sensitivities of bone SPECT/CT, labeled leukocyte SPECT/CT, and dual-isotope SPECT/CT were similar at 94%, 87%, and 95%, respectively. The specificity of dual-isotope SPECT/CT (94%) was significantly higher than that of bone SPECT/CT (47%) and labeled leukocyte SPECT/CT (68%) individually (*37*).

Scenario 34: Diagnosis of foot osteomyelitis in diabetic patients, combined labeled leukocyte/bone marrow scintigraphy (Score 8 – Appropriate)

There were no data in the systematic reviews on the role of combined labeled leukocyte/bone marrow scintigraphy for diagnosing diabetic foot osteomyelitis. Two publications evaluated the role of the combined test in diabetic patients with a neuropathic joint, both using ^{111}In-labeled leukocytes. In one investigation, only planar imaging was performed. The test was 95% accurate (*40*). In the second investigation, SPECT/CT was performed and the accuracy was 96% (*37*).

Scenario 35: Diagnosis of foot osteomyelitis in diabetic patients, ^{18}F-FDG PET and PET/CT (Score 8 – Appropriate)

Two systematic reviews evaluated the accuracy of ^{18}F-FDG PET and PET/CT for the diagnosis of osteomyelitis involving diabetic foot ulcers. The level of evidence was fair. One systematic review included 4 studies with 178 cases, 2 performed with PET and 2 with PET/CT. The pooled sensitivity was 74% (95% CI, 0.60–0.85) and the pooled specificity was 91% (95% CI, 0.85–0.96) (*41*).

In the second systematic review, PET alone was used in 4 studies and PET/CT in 2. The pooled sensitivity was 89% and the pooled specificity was 92% (95% CI, 0.85–0.96). In the 2 studies that used PET/CT, the sensitivity was 81% and 88% and the specificity was 93% and 97%, similar to the overall pooled results. The pooled sensitivity and specificity of ^{111}In-labeled leukocyte scintigraphy were 92% and 75%, respectively. The pooled sensitivity and specificity of ^{99m}Tc-labeled leukocyte scintigraphy were 91% and 92%, respectively (*36*).

SUMMARY OF RECOMMENDATIONS

Labeled leukocyte scintigraphy, alone or in combination with bone scintigraphy, and ^{18}F-FDG PET and PET/CT are the most appropriate nuclear medicine imaging tests for diagnosing diabetic foot osteomyelitis. Combined labeled leukocyte/marrow scintigraphy accurately diagnoses osteomyelitis in the presence of the neuropathic joint and is appropriate for this indication. Labeled leukocyte scintigraphy and ^{18}F-FDG PET/CT are superior to bone and ^{67}Ga scintigraphy, alone and in combination, and therefore the latter 2 studies should not be used for diagnosing diabetic foot osteomyelitis.

DIAGNOSIS OF PJI OF THE HIP AND KNEE

Introduction

The prevalence of PJI up to 2 y following hip replacement is 1.63% and following knee replacement is 1.55%. Both procedures have a prevalence greater than 2% at 10 y (*42*,*43*). Both the incidence and the prevalence of PJI are increasing due to increased use of the procedure and increased life expectancy of patients (*44*). Diagnosing PJI and differentiating it from other causes of prosthetic joint failure is extremely important because although many causes of prosthetic failure can be treated with single-stage exchange arthroplasty during one hospital admission with one surgical intervention, the treatment of PJI usually requires longer and more complicated procedures. An excisional arthroplasty is performed followed by weeks to months of antibiotic treatment and eventually a revision arthroplasty. A sensitive but nonspecific test can lead to multiple costly operations when a single intervention would have sufficed. A specific, but insensitive, test will result in additional surgical interventions because undiagnosed infection will cause any revision implant to fail with potentially serious consequences (*45*).

TABLE 6
Clinical Scenarios for the Diagnosis of PJI of the Hip and Knee

Scenario no.	Description	Appropriateness	Score
Hip			
36	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	May be appropriate	4
37	^{67}Ga scintigraphy	Rarely appropriate	2
38	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	2
39	Labeled leukocyte scintigraphy	Appropriate	7
40	Combined labeled leukocyte/bone scintigraphy	Appropriate	7
41	Combined labeled leukocyte/bone marrow scintigraphy	Appropriate	7
42	^{18}F-FDG PET and PET/CT	Appropriate	7
Knee			
43	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	May be appropriate	4
44	^{67}Ga scintigraphy	Rarely appropriate	2
45	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	2
46	Labeled leukocyte scintigraphy	May be appropriate	6
47	Combined labeled leukocyte/bone scintigraphy	Appropriate	8
48	Combined labeled leukocyte/bone marrow scintigraphy	Appropriate	8
49	^{18}F-FDG PET and PET/CT	May be appropriate	6

Background

Pain is usually present. Fever is variable, with the incidence ranging from less than 5% to more than 40% of patients. Leukocytosis is a poor predictor of infection. After primary uncomplicated arthroplasty, the C-reactive protein level remains elevated for up to 3 wk, and the erythrocyte sedimentation rate can remain elevated for up to 1 y. Joint aspiration with culture, the definitive preoperative diagnostic procedure, is specific but its sensitivity is variable. Over the years, several nuclear medicine imaging studies, including bone, ^{67}Ga, labeled leukocyte, and, more recently, ^{18}F-FDG, have been used to improve the preoperative diagnosis of PJI (*2*,*45*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of PJI of the hip and knee, along with final AUC scores, are presented in Table 6.

Scenario 36: Diagnosis of PJI of the hip, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 4 – May be Appropriate)

One systematic review focused on bone scintigraphy for diagnosing PJI of the hip (*46*). The level of evidence was fair. The pooled sensitivity was 80% (95% CI, 0.72–0.86) and the pooled specificity was 69% (95% CI, 0.64–0.73). None of the studies included in the review evaluated SPECT or SPECT/CT. Bone scintigraphy was less sensitive than labeled leukocyte scintigraphy (88%) and ^{18}F-FDG PET (86%), but more sensitive than combined labeled leukocyte/marrow scintigraphy (69%). Bone scintigraphy was less specific than labeled leukocyte scintigraphy (92%), combined labeled leukocyte/bone marrow scintigraphy (96%), and ^{18}F-FDG-PET (93%).

Scenario 37: Diagnosis of PJI of the hip, ^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

There were no systematic reviews on the role of ^{67}Ga scintigraphy for diagnosing PJI of the hip. The sensitivity and specificity of ^{67}Ga scintigraphy for PJI of the hip range from 37% to 83% and from 77% to 100%, respectively (*47*). The most recent data on ^{67}Ga scintigraphy for diagnosing PJI of the hip are more than 25 y old, as this test has been replaced by combined labeled leukocyte/bone marrow and ^{18}F-FDG PET and PET/CT. It is the expert opinion of the workgroup that ^{67}Ga scintigraphy should not be used for diagnosing PJI of the hip.

Scenario 38: Diagnosis of PJI of the hip, combined bone/^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

One systematic review evaluated the accuracy of combined bone/^{67}Ga scintigraphy for the diagnosis of PJI of the hip (*46*). None of the studies in this review included SPECT or SPECT/CT. The pooled sensitivity was 59% (95% CI, 0.42–0.74) and the pooled specificity was 97% (95% CI, 0.91–0.99). The combined test was significantly more specific ($P < 0.0001$) but significantly less sensitive ($P = 0.013$) than bone scintigraphy alone. It is the expert opinion of the workgroup that combined bone/^{67}Ga scintigraphy should not be used for diagnosing PJI of the hip.

Scenario 39: Diagnosis of PJI of the hip, labeled leukocyte scintigraphy (Score 7 – Appropriate)

One systematic review addressed the diagnosis of PJI of the hip with labeled leukocyte scintigraphy (*46*). The level of evidence was fair. The pooled sensitivity of labeled leukocyte scintigraphy was 88% and the pooled specificity was 85%. Labeled leukocyte scintigraphy was more sensitive (88% vs. 80%) and significantly more specific ($P < 0.0001$) (85% vs. 69%) than bone scintigraphy.

Scenario 40: Diagnosis of PJI of the hip, combined labeled leukocyte/bone scintigraphy (Score 7 – Appropriate)

One systematic review addressed the diagnosis of PJI of the hip with combined labeled leukocyte/bone scintigraphy (*46*). The level of evidence was fair. The pooled sensitivity of combined labeled leukocyte/bone scintigraphy was 77% and the pooled specificity

was 95%, values that were not significantly different from those of labeled leukocyte scintigraphy alone.

Scenario 41: Diagnosis of PJI of the hip, combined labeled leukocyte/bone marrow scintigraphy (Score 7 – Appropriate)

One systematic review addressed the diagnosis of PJI of the hip with combined labeled leukocyte/bone marrow scintigraphy (*46*). The level of evidence was fair. The pooled sensitivity was 69% and the pooled specificity was 96%. The test was significantly less sensitive than labeled leukocyte scintigraphy alone ($P < 0.0001$). The test was more specific than labeled leukocyte scintigraphy alone, but the difference was not significant.

Scenario 42: Diagnosis of PJI of the hip, ^{18}F-FDG PET and PET/CT (Score 7 – Appropriate)

Three systematic reviews addressed the role of ^{18}F-FDG PET for diagnosing PJI of the hip (*46*,*48*,*49*). The level of evidence was fair for all 3. In one review, the pooled sensitivity and the pooled specificity were 86% and 93%, respectively. ^{18}F-FDG-PET was significantly more specific than bone scintigraphy and significantly more sensitive than combined labeled leukocyte/bone marrow scintigraphy. There was no significant difference in sensitivity or specificity between ^{18}F-FDG-PET and labeled leukocyte scintigraphy alone (*46*). In the second review, the pooled sensitivity and the pooled specificity of ^{18}F-FDG-PET were both 88% (*48*). In the third review, the pooled sensitivity and the pooled specificity of ^{18}F-FDG-PET were 83% and 90%, respectively (*49*).

The following clinical scenarios address the diagnosis of PJI of the knee.

Scenario 43: Diagnosis of PJI of the knee, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 4 – May be Appropriate)

One systematic review evaluated bone scintigraphy for diagnosing PJI of the knee (*50*). The level of evidence was fair. The pooled sensitivity of bone scintigraphy was 93% and the pooled specificity was 56%. The specificity was less than that of labeled leukocyte scintigraphy (77%), combined labeled leukocyte/bone marrow scintigraphy (95%), and ^{18}F-FDG (84%).

Scenario 44: Diagnosis of PJI of the knee, ^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews addressed the role of ^{67}Ga scintigraphy for the diagnosis of PJI of the knee, and there are no data on this topic published within the past 25 y. This test has been replaced by combined labeled leukocyte/marrow and ^{18}F-FDG PET and PET/CT. It is the expert opinion of the workgroup that ^{67}Ga scintigraphy should not be used for diagnosing PJI of the knee.

Scenario 45: Diagnosis of PJI of the knee, combined bone/^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews addressed the role of combined bone/^{67}Ga scintigraphy for the diagnosis of PJI of the knee. Published data on combined bone/^{67}Ga scintigraphy for PJI are more than 25 y old. This test has been replaced by combined labeled leukocyte/bone marrow scintigraphy and ^{18}F-FDG PET and PET/CT. It is the expert opinion of the workgroup that combined bone/^{67}Ga scintigraphy should not be used for diagnosing PJI of the knee.

Scenario 46: Diagnosis of PJI of the knee, labeled leukocyte scintigraphy (Score 6 – May be Appropriate)

One systematic review included labeled leukocyte scintigraphy for diagnosing PJI of the knee (*50*). The level of evidence was fair. The pooled sensitivity was 88% and the pooled specificity was 77%. Labeled leukocyte scintigraphy was significantly more sensitive ($P = 0.01$) than ^{18}F-FDG PET (70%), but was not significantly more sensitive than bone scintigraphy (93%), combined labeled leukocyte/bone scintigraphy (93%), and combined labeled leukocyte/bone marrow scintigraphy (80%).

Scenario 47: Diagnosis of PJI of the knee, combined labeled leukocyte/bone scintigraphy (Score 8 – Appropriate)

One systematic review included the diagnosis of PJI of the knee by using combined labeled leukocyte/bone scintigraphy (*50*). The pooled sensitivity was 93% and the pooled specificity was 82%. These values were not significantly different from the sensitivity and specificity of labeled leukocyte scintigraphy alone, which were 88% and 77%, respectively.

Scenario 48: Diagnosis of PJI of the knee, combined labeled leukocyte/bone marrow scintigraphy (Score 8 – Appropriate)

One systematic review addressed the role of combined labeled leukocyte/bone marrow scintigraphy for diagnosing PJI of the knee (*50*). The level of evidence was fair. The pooled sensitivity was 80% and the pooled specificity was 93%. Combined labeled leukocyte/bone marrow scintigraphy was significantly more specific than bone scintigraphy ($P < 0.001$), leukocyte scintigraphy ($P < 0.001$), and ^{18}F-FDG PET ($P < 0.001$). There were no significant differences in specificity between combined labeled leukocyte/bone marrow scintigraphy and combined labeled leukocyte/bone scintigraphy. There were no significant differences in sensitivity among combined labeled leukocyte/bone marrow, combined labeled leukocyte/bone, labeled leukocyte scintigraphy, and ^{18}F-FDG PET.

Scenario 49: Diagnosis of PJI of the knee, ^{18}F-FDG PET and PET/CT (Score 6 – May be Appropriate)

Three systematic reviews analyzed the diagnosis of PJI of the knee with ^{18}F-FDG PET and PET/CT (*48–50*). The level of evidence was fair in all 3. In one review, the pooled sensitivity was 72% (95% CI, 0.58–0.84) and the pooled specificity was 80% (95% CI, 0.71–0.88) (*48*). In the second review, the pooled sensitivity was 90% and the pooled specificity was 75% (*49*). In the third review, the pooled sensitivity was 70% (95% CI, 0.56–0.81) and the pooled specificity was 84% (95% CI, 0.76–0.90) (*50*).

SUMMARY OF RECOMMENDATIONS

Combined leukocyte/bone scintigraphy, combined leukocyte/bone marrow scintigraphy, and ^{18}F-FDG PET and PET/CT are the most appropriate procedures for diagnosing PJI of the hip and knee. ^{18}F-FDG PET and PET/CT are the most sensitive, and combined leukocyte/bone marrow scintigraphy is the most specific of the tests. Bone scintigraphy may be useful as a screening test. ^{67}Ga scintigraphy and combined bone/^{67}Ga scintigraphy have been replaced by labeled leukocyte scintigraphy and ^{18}F-FDG PET PET/CT and should not be used for diagnosing PJI of the hip and knee.

DIAGNOSIS OF PJI OF THE SHOULDER

Introduction

Shoulder joint replacement was first performed in the United States in the 1950s to treat severe shoulder fractures, and over the

TABLE 7
Clinical Scenarios for the Diagnosis of PJI of the Shoulder

Scenario no.	Description	Appropriateness	Score
50	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	May be appropriate	4
51	^{67}Ga scintigraphy	Rarely appropriate	2
52	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	2
53	Labeled leukocyte scintigraphy	May be appropriate	5
54	Combined labeled leukocyte/bone scintigraphy	May be appropriate	5
55	Combined labeled leukocyte/bone marrow scintigraphy	May be appropriate	5
56	^{18}F-FDG PET and PET/CT	May be appropriate	5

years this procedure has come to be useful for a variety of painful shoulder conditions (*51*). Postoperative complications develop in nearly 25% of shoulder arthroplasties, about half of which require revision surgery. The standard diagnostic evaluation consists of history, physical examination, and laboratory tests, including white blood cell count, C-reactive protein level, and erythrocyte sedimentation rate. Imaging tests typically include plain radiographs, CT, and ultrasonography (*52*).

Background

PJI is a serious complication of shoulder arthroplasty, with a reported incidence between 1% and 10%. Risk factors include rheumatoid arthritis, previous shoulder surgery, diabetes, and immunosuppression. These infections are classified as early (≤3 mo), delayed (3–24 mo), and late (<24 mo) and can be further classified on the basis of duration of symptoms as acute (<6 wk) or chronic (>6 wk). Acute infection typically presents as septic arthritis with erythema, swelling, pain, and abnormal laboratory test results and is readily diagnosed. The diagnosis of chronic infection is more challenging. Definitive diagnosis is made via arthrocentesis (*52*). Data on nuclear medicine imaging in the workup of complications of shoulder arthroplasty are limited.

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of PJI of the shoulder, along with final AUC scores, are presented in Table 7.

Scenario 50: Diagnosis of PJI of the shoulder, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 4 – May be Appropriate)

The role of bone scintigraphy for diagnosing PJI of the shoulder was not addressed in the systematic reviews. The evolution of periprosthetic uptake around the various types of shoulder arthroplasties has not been well established. Bone scintigraphy with SPECT/CT provides information about different types of mechanical complications of shoulder arthroplasty (*53*). There are no data on the role of bone scintigraphy for diagnosing PJI of the shoulder. It is the expert opinion of the workgroup that, based on the high sensitivity of bone scintigraphy in general, this test may be a good "rule-out" test; that is, a negative result excludes infection with a high degree of certainty.

Scenario 51: Diagnosis of PJI of the shoulder, ^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

There are no systematic reviews on the role of ^{67}Ga scintigraphy for diagnosing PJI of the shoulder. The most recent data on ^{67}Ga scintigraphy for diagnosing PJIs, which are more than 25 y old, are limited to lower extremity arthroplasties. This test has been largely replaced by combined labeled leukocyte/bone marrow scintigraphy and ^{18}F-FDG PET and PET/CT and it is the expert opinion of the workgroup that ^{67}Ga scintigraphy should not be used for diagnosing PJI of the shoulder.

Scenario 52: Diagnosis of PJI of the shoulder, combined bone/^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

No systematic reviews addressed the role of combined bone/^{67}Ga scintigraphy for diagnosing PJI of the shoulder. Few, if any, studies have been published on combined bone/^{67}Ga scintigraphy over the past 25 y, none of which address its role in diagnosing PJI of the shoulder. Combined bone/^{67}Ga scintigraphy has largely been replaced by combined labeled leukocyte/bone marrow scintigraphy and ^{18}F-FDG PET and PET/CT and it is the expert opinion of the workgroup that combined bone/^{67}Ga scintigraphy should not be used for diagnosing PJI of the shoulder.

Scenario 53: Diagnosis of PJI of the shoulder, labeled leukocyte scintigraphy (Score 5 – May be Appropriate)

No systematic reviews addressed the role of labeled leukocyte scintigraphy for diagnosing PJI of the shoulder. In one small series, ^{99m}Tc-labeled leukocyte scintigraphy with SPECT/CT confirmed the presence of periprosthetic infection and involvement of soft tissues of the arm and of ipsilateral axillary lymph nodes (*51*). It is the expert opinion of the workgroup that labeled leukocyte scintigraphy may be useful for diagnosing PJI of the shoulder.

Scenario 54: Diagnosis of PJI of the shoulder, combined labeled leukocyte/bone scintigraphy (Score 5 – May be Appropriate)

No systematic reviews addressed the role of combined labeled leukocyte/bone scintigraphy for diagnosing periprosthetic shoulder infection. In one investigation, as part of a larger series, combined labeled leukocyte/bone scintigraphy was useful for diagnosing PJI of the shoulder (*54*). It is the expert opinion of the workgroup that combined labeled leukocyte/bone scintigraphy may be useful for diagnosing PJI of the shoulder.

Scenario 55: Diagnosis of PJI of the shoulder, combined labeled leukocyte/bone marrow scintigraphy (Score 5 – May be Appropriate)

No systematic reviews addressed the role of combined labeled leukocyte/bone marrow scintigraphy for diagnosing PJI of the shoulder. In one investigation combined labeled leukocyte/bone marrow scintigraphy with SPECT/CT was 18% sensitive (2/11)

TABLE 8
Clinical Scenarios for the Diagnosis of Septic Arthritis

Scenario no.	Description	Appropriateness	Score
57	Bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP)	May be appropriate	4
58	^{67}Ga scintigraphy	Rarely appropriate	2
59	Combined bone/^{67}Ga scintigraphy	Rarely appropriate	2
60	Labeled leukocyte scintigraphy	May be appropriate	6
61	Combined labeled leukocyte/bone scintigraphy	May be appropriate	6
62	Combined labeled leukocyte/bone marrow scintigraphy	May be appropriate	6
63	^{18}F-FDG PET and PET/CT	May be appropriate	6

and 100% specific (18/18) for PJI of the shoulder (*55*). It is the expert opinion of the workgroup that combined labeled leukocyte/bone marrow scintigraphy with SPECT/CT may be useful in the diagnostic workup of PJI of the shoulder. Although a negative result does not exclude infection, a positive result makes it likely that infection is present.

Scenario 56: Diagnosis of PJI of the shoulder, ^{18}F-FDG PET and PET/CT (Score 5 – May be Appropriate)

No systematic reviews addressed the role of ^{18}F-FDG PET and PET/CT for diagnosing PJI of the shoulder. In an investigation of 86 patients with suspected chronic PJI of the shoulder, the sensitivity and specificity of ^{18}F-FDG PET/CT were 14% (3/22) and 91% (58/64), respectively (*56*). It is the expert opinion of the workgroup that ^{18}F-FDG PET/CT may be useful in the diagnostic workup of PJI of the shoulder. Although a negative result does not exclude infection, a positive result makes it likely that infection is present.

SUMMARY OF RECOMMENDATIONS

There are few data on nuclear medicine imaging of PJI of the shoulder. Because of its high sensitivity, bone scintigraphy may be useful for excluding infection. Labeled leukocyte imaging may be helpful for identifying infection in the surrounding soft tissues. Combined labeled leukocyte/bone scintigraphy may be useful in the diagnosis of PJI of the shoulder. Combined labeled leukocyte/bone marrow scintigraphy and ^{18}F-FDG PET and PET/CT are especially useful when abnormal, as they have a high positive predictive value. ^{67}Ga scintigraphy and combined bone/^{67}Ga scintigraphy have largely been replaced by combined labeled leukocyte/bone marrow imaging and ^{18}F-FDG PET and PET/CT for PJI in general and it is the expert opinion of the workgroup that they should not be used for diagnosing PJI of the shoulder.

DIAGNOSIS OF SEPTIC ARTHRITIS

Introduction

Septic arthritis is the invasion of a joint and synovial fluid by an infectious agent. It has an annual incidence of 10/100,000 individuals in the United States and is more common among individuals with rheumatoid arthritis or a prosthetic joint, factors that can increase the incidence up to 7 fold. Patients with diabetes mellitus and HIV also are at increased risk for septic arthritis (*57*,*58*). Septic arthritis can involve multiple joints, causing rapid joint destruction. It is a medical and surgical emergency that affects both the early and the chronic functional prognosis of the involved joint, in addition to overall patient prognosis. In patients with high clinical suspicion of septic arthritis, prompt diagnosis to facilitate appropriate antibiotic management is essential, since cartilage can be destroyed within days, and in-hospital mortality of untreated infections can be as high as 15% (*59*).

Background

The typical presentation of septic arthritis is that of pain involving a single joint, combined with erythema, soft-tissue swelling, and diminished range of motion. Fever, chills, general weakness, and headaches are often present (*60*). The diagnosis of septic arthritis is challenging. Noninfectious arthritis and infectious (septic) arthritis can have identical or very similar clinical presentations. Acute monoarticular arthritis in adults has multiple potential causes, including infection, crystalloid arthropathies, rheumatoid arthritis, connective tissue disease, inflammatory bowel disease, sarcoidosis, lupus, vasculitis, and trauma (*60*,*61*). Clinical evaluation and aspiration of joint fluid are key to diagnosis. The reference standard for the diagnosis of septic arthritis is a positive culture result from joint aspirate samples. However, a negative culture result does not exclude the diagnosis, especially if the patient is already receiving antibiotic therapy (*62*,*63*).

Clinical Scenarios and AUC Scores

Clinical scenarios for the diagnosis of septic arthritis, along with final AUC scores, are presented in Table 8.

Scenario 57: Diagnosis of septic arthritis, bone scintigraphy (^{99m}Tc-MDP or ^{99m}Tc-HDP) (Score 4 – May be Appropriate)

There are no systematic reviews on the role of bone scintigraphy in the diagnosis of septic arthritis. In one of the earliest investigations, bone scintigraphy correctly identified all 6 cases of septic arthritis (*64*). In an investigation of 21 suspected sites of septic arthritis, bone scintigraphy correctly identified all 10 sites of septic arthritis (100% sensitivity) and the results were true-negative in 6 of 7 uninfected joints (85% specificity) (*65*). In another study of 15 patients, however, bone scintigraphy could not reliably differentiate septic from rheumatoid arthritis (*66*). It is the expert opinion of the workgroup that although bone scintigraphy is not specific, it is a sensitive modality and thus of value as a "rule-out" test.

Scenario 58: Diagnosis of septic arthritis, ^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

There are no systematic reviews on the role of ^{67}Ga scintigraphy in the diagnosis of septic arthritis and there are no recent data on its role for this indication. In one investigation, ^{67}Ga scintigraphy gave positive results in all 6 cases of septic arthritis (*63*). In

another study, the investigators found that it was not possible to distinguish septic from rheumatoid arthritis (*66*). ^{67}Ga scintigraphy has been replaced by labeled leukocyte scintigraphy and ^{18}F-FDG PET and PET/CT for most indications in musculoskeletal infection. It is the expert opinion of the workgroup that this agent should not be used for diagnosing septic arthritis.

Scenario 59: Diagnosis of septic arthritis, combined bone/^{67}Ga scintigraphy (Score 2 – Rarely Appropriate)

There are no systematic reviews on the role of combined bone/^{67}Ga scintigraphy for the diagnosis of septic arthritis. Available data suggest that it is not possible to differentiate between septic and inflammatory arthritis with combined bone/^{67}Ga imaging (*66*). It is the expert onion of the workgroup that this test should not be used for diagnosing septic arthritis.

Scenario 60: Diagnosis of septic arthritis, labeled leukocyte scintigraphy (Score 6 – May be Appropriate)

There are no systematic reviews on the role of labeled leukocyte scintigraphy for the diagnosis of septic arthritis. In one investigation the test was 80% sensitive and 83% specific (*67*). Labeled leukocytes also accumulate in inflammatory arthritis (*68*). Data comparing labeled leukocyte scintigraphy in septic and inflammatory arthritis are lacking. It is the expert opinion of the workgroup that labeled leukocyte scintigraphy may not be able to differentiate between septic and inflammatory arthritis.

Scenario 61: Diagnosis of septic arthritis, combined labeled leukocyte/bone scintigraphy (Score 6 – May be Appropriate)

There are no systematic reviews on the role of combined labeled leukocyte/bone scintigraphy for the diagnosis of septic arthritis. This test is performed to diagnose osteomyelitis, not septic arthritis. In view of the lack of data for diagnosing septic arthritis, and because it may not be possible to differentiate between infectious and inflammatory arthritis with either of these agents individually, it is the expert opinion of the workgroup that combined labeled leukocyte/bone scintigraphy should be reserved for situations in which osteomyelitis is a diagnostic consideration.

Scenario 62: Diagnosis of septic arthritis, combined labeled leukocyte/bone marrow scintigraphy (Score 6 – May be Appropriate)

There are no systematic reviews on the role of combined labeled leukocyte/marrow scintigraphy for diagnosing septic arthritis. This test is performed to diagnose osteomyelitis, not septic arthritis. It is the expert opinion of the workgroup that combined labeled leukocyte/bone marrow scintigraphy should be reserved for those situations in which osteomyelitis is a diagnostic consideration.

Scenario 63: Diagnosis of septic arthritis, ^{18}F-FDG PET and PET/CT (Score 6 – May be Appropriate)

There are no systematic reviews on the role of ^{18}F-FDG PET and PET/CT for the diagnosis of septic arthritis and there are few data on its use for diagnosing septic arthritis. ^{18}F-FDG accumulates in a variety of inflammatory arthridities, including rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, and therefore it may not be possible to differentiate septic from inflammatory arthritis (*69*). Given the high sensitivity of ^{18}F-FDG PET and PET/CT for inflammation and infection in general, it is the expert opinion of the workgroup that a negative ^{18}F-FDG PET and PET/CT result may be useful for excluding septic arthritis.

SUMMARY OF RECOMMENDATIONS

Because of their high sensitivity, bone scintigraphy and ^{18}F-FDG PET and PET/CT are useful rule-out tests for septic arthritis. Labeled leukocyte scintigraphy alone and in combination with bone or bone marrow scintigraphy may be helpful when the results of these tests are inconclusive and when osteomyelitis is a diagnostic consideration. ^{67}Ga alone and in combination with bone scintigraphy should not be used for diagnosing septic arthritis.

REFERENCES

1. Palestro CJ. Molecular imaging of infection: the first fifty years. *Sem Nucl Med.* 2020;50:23–34.
2. Palestro CJ. Radionuclide imaging of musculoskeletal infection: a review. *J Nucl Med.* 2016;57:1406–1412.
3. Protecting Access to Medicare Act of 2014, Pub L No. 113-93, 128 Stat 1040 (2014).
4. Fitch K, Bernstein SJ, Aguilar MD, Burnand B. *The RAND/UCLA Appropriateness Method User's Manual.* Santa Monica, CA: RAND; 2001.
5. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. *Clinical Practice Guidelines We Can Trust.* Washington, DC: National Academies Press; 2011.
6. Pacific Northwest Evidence-Based Practice Center. *Systematic Review: Nuclear Medicine Imaging Techniques for Infectious Diseases and Inflammatory Conditions.* Portland, OR: Oregon Health and Science University; 2018.
7. Shea BJ, Bouter LM, Peterson J, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). *PLoS One.* 2007;2:e1350.
8. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155:529–536.
9. *AQA Principles for Appropriateness Criteria*. London, U.K.: Assessment and Qualifications Alliance; 2009.
10. Raghavan M, Lazzeri E, Palestro CJ. Imaging of spondylodiscitis. *Semin Nucl Med.* 2018;48:131–147.
11. Dunn RN, Castelein S, Held M. Impact of HIV on spontaneous spondylodiscitis. *Bone Joint J.* 2019;101-B:617–620.
12. Legrand E, Flipo R-M, Guggenbuhl P, et al. Management of nontuberculous infectious discitis: treatments used in 110 patients admitted to 12 teaching hospitals in France. *Joint Bone Spine.* 2001;68:504–509.
13. Gratz S, Dorner J, Oestmann JW, et al. 67Ga-citrate and 99Tcm-MDP for estimating the severity of vertebral osteomyelitis. *Nucl Med Commun.* 2000;21: 111–120.
14. Love C, Patel M, Lonner BS, Tomas MB, Palestro CJ. Diagnosing spinal osteomyelitis: a comparison of bone and Ga-67 scintigraphy and magnetic resonance imaging. *Clin Nucl Med.* 2000;25:963–977.
15. Gratz S, Dorner J, Fischer U, et al. 18F-FDG hybrid PET in patients with suspected spondylitis. *Eur J Nucl Med Mol Imaging.* 2002;29:516–524.
16. Fuster D, Solà O, Soriano A, et al. A prospective study comparing whole-body FDG PET/CT to combined planar bone scan with 67Ga SPECT/CT in the diagnosis of spondylodiskitis. *Clin Nucl Med.* 2012;37:827–832.
17. Tamm AS, Abele JT. Bone and gallium single-photon emission computed tomography-computed tomography is equivalent to magnetic resonance imaging in the diagnosis of infectious spondylodiscitis: a retrospective study. *Can Assoc Radiol J.* 2017;68:41–46.
18. Termaat MF, Raijmakers PG, Scholten HJ, Bakker FC, Patka P, Haarman HJ. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. *J Bone Joint Surg Am.* 2005;87:2464–2471.
19. Palestro CJ, Kim CK, Swyer AJ, Vallabhajosula S, Goldsmith SJ. Radionuclide diagnosis of vertebral osteomyelitis: indium-111-leukocyte and technetium-99m-methylene diphosphonate bone scintigraphy. *J Nucl Med.* 1991;32:1861–1865.
20. Prodromou ML, Ziakas PD, Poulou LS, Karsaliakos P, Thanos L, Mylonakis E. FDG PET is a robust tool for the diagnosis of spondylodiscitis: a meta-analysis of diagnostic data. *Clin Nucl Med.* 2014;39:330–335.
21. Treglia G, Pascale M, Lazzeri E, van der Bruggen W, Delgado Bolton RC, Glaudemans AWJM. Diagnostic performance of 18F-FDG PET/CT in patients with spinal infection: a systematic review and a bivariate meta-analysis. *Eur J Nucl Med Mol Imaging.* 2020;47:1287–1301.
22. Rutenberg TF, Baruch Y, Ohana N, et al. The role of 18F-fluorodeoxyglucose positron-emission tomography/computed tomography in the diagnosis of postoperative hardware-related spinal infections. *Isr Med Assoc J.* 2019;21:532–537.

23. Hadjipavlou AG, Cesani-Vazquez F, Villaneuva-Meyer J, et al. The effectiveness of gallium citrate Ga 67 radionuclide imaging in vertebral osteomyelitis revisited. *Am J Orthop.* 1998;27:179–183.
24. Palestro CJ. Nuclear medicine imaging of osteomyelitis: white blood cell, monoclonal antibody, or bacterial imaging? In: Signore A, Quintero AM, eds. *Diagnostic Imaging of Infections and Inflammatory Diseases: A Multidisciplinary Approach.* New York, NY: John Wiley & Sons; 2013:168–186.
25. Schauwecker DS. The scintigraphic diagnosis of osteomyelitis. *AJR.* 1992;158:9–18.
26. Palestro CJ, Torres MA. Radionuclide imaging in orthopedic infections. *Semin Nucl Med.* 1997;27:334–345.
27. Wang GL, Zhao K, Liu ZF, Dong MJ, Yang SY. A meta-analysis of fluorodeoxyglucose-positron emission tomography versus scintigraphy in the evaluation of suspected osteomyelitis. *Nucl Med Commun.* 2011;32:1134–1142.
28. Palestro CJ, Roumanas P, Swyer AJ, Kim CK, Goldsmith SJ. Diagnosis of musculoskeletal infection using combined In-111 labeled leukocyte and Tc-99m SC marrow imaging. *Clin Nucl Med.* 1992;17:269–273.
29. Achong DM, Oates E. The computer-generated bone marrow subtraction image: a valuable adjunct to combined In-111 WBC/Tc-99m in sulfur colloid scintigraphy for musculoskeletal infection. *Clin Nucl Med.* 1994;19:188–193.
30. Lavery LA, Ryan EC, Ahn J, et al. The infected diabetic foot: re-evaluating the Infectious Diseases Society of America diabetic foot infection classification. *Clin Infect Dis.* 202010;70:1573–1579.
31. Palestro CJ, Love C. Nuclear medicine and diabetic foot infections. *Semin Nucl Med.* 2009;39:52–65.
32. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis.* 2008;47:519–527.
33. Johnson JE, Kennedy EJ, Shereff MJ, Patel NC, Collier BD. Prospective study of bone, indium-111-labeled white blood cell, and gallium-67 scanning for the evaluation of osteomyelitis in the diabetic foot. *Foot Ankle Int.* 1996;17:10–16.
34. Aslangul E, M'bemba J, Caillat-Vigneron N, et al. Diagnosing diabetic foot osteomyelitis in patients without signs of soft tissue infection by coupling hybrid 67Ga SPECT/CT with bedside percutaneous bone puncture. *Diabetes Care.* 2013;36:2203–2210.
35. Delcourt A, Huglo D, Prangere T, et al. Comparison between Leukoscan (sulesomab) and gallium-67 for the diagnosis of osteomyelitis in the diabetic foot. *Diabetes Metab.* 2005;31:125–133.
36. Lauri C, Tamminga M, Glaudemans A, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. *Diabetes Care.* 2017;40:1111–1120.
37. Heiba SI, Kolker D, Mocherla B, et al. The optimized evaluation of diabetic foot infection by dual isotope SPECT/CT imaging protocol. *J Foot Ankle Surg.* 2010;49:529–536.
38. Devillers A, Moisan A, Hennion F, Garin E, Poirier JY, Bourguet P. Contribution of technetium-99m hexamethylpropylene amine oxime labelled leucocyte scintigraphy to the diagnosis of diabetic foot infection. *Eur J Nucl Med.* 1998;25:132–138.
39. Poirier JY, Garin E, Derrien C, et al. Diagnosis of osteomyelitis in the diabetic foot with a 99mTc-HMPAO leucocyte scintigraphy combined with a 99mTc-MDP bone scintigraphy. *Diabetes Metab.* 2002;28(6 Pt 1):485–490.
40. Palestro CJ, Mehta HH, Patel M, et al. Marrow versus infection in the Charcot joint: indium-111 leukocyte and technetium-99m sulfur colloid scintigraphy. *J Nucl Med.* 1998;39:346–350.
41. Treglia G, Sadeghi R, Annunziata S, et al. Diagnostic performance of Fluorine-18-Fluorodeoxyglucose positron emission tomography for the diagnosis of osteomyelitis related to diabetic foot: a systematic review and a meta-analysis. *Foot (Edinb).* 2013;23:140–148.
42. Ong KL, Kurtz SM, Lau E, Bozic KJ, Berry DJ, Parvizi J. Prosthetic joint infection risk after total hip arthroplasty in the Medicare population. *J Arthroplasty.* 2009;24(6 Suppl):105–109.
43. Kurtz SM, Ong KL, Lau E, Bozic KJ, Berry D, Parvizi J. Prosthetic joint infection risk after TKA in the Medicare population. *Clin Orthop Relat Res.* 2010;468:52–56.
44. Kurtz SM, Lau E, Schmier J, Ong KL, Zhao K, Parvizi J. Infection burden for hip and knee arthroplasty in the United States. *J Arthroplasty.* 2008;23:984–991.
45. Love C, Marwin SE, Palestro CJ. Nuclear medicine and the infected joint replacement. *Semin Nucl Med.* 2009;39:66–78.
46. Verberne SJ, Raijmakers PG, Temmerman OP. The accuracy of imaging techniques in the assessment of periprosthetic hip infection: a systematic review and meta-analysis. *J Bone Joint Surg Am.* 2016;98:1638–1645.
47. Palestro CJ. Nuclear medicine and the failed joint replacement: past, present, and future. *World J Radiol.* 2014;6:446–458.
48. Jin H, Yuan L, Li C, et al. Diagnostic performance of FDG PET or PET/CT in prosthetic infection after arthroplasty: a meta-analysis. *Q J Nucl Med Mol Imaging.* 2014;58:85–93.
49. Kwee TC, Kwee RM, Alavi A. FDG-PET for diagnosing prosthetic joint infection: systematic review and metaanalysis. *Eur J Nucl Med Mol Imaging.* 2008;35:2122–2132.
50. Verberne SJ, Sonnega RJ, Temmerman OP, et al. What is the accuracy of nuclear imaging in the assessment of periprosthetic knee infection? A meta-analysis. *Clin Orthop.* 2017;475:1395–1410.
51. Suárez JP, Domínguez ML, Zeidán N, et al. Complications of shoulder arthroplasty: added value of SPECT/CT imaging. *Rev Esp Med Nucl Imagen Mol.* 2019;38:234–237.
52. Wiater BP, Moravek Jr JE, Wiater JM. The evaluation of the failed shoulder arthroplasty. *J Shoulder Elbow Surg.* 2014;23:745–758.
53. Thélu-Vanysacker M, Frédéric P, Charles-Edouard T, Alban B, Nicolas B, Tanguy B. SPECT/CT in postoperative shoulder pain. *Semin Nucl Med.* 2018;48:469–482.
54. Johnson JA, Christie MJ, Sandler MP, Parks Jr PF, Homra L, Kaye JJ. Detection of occult infection following total joint arthroplasty using sequential technetium-99m HDP bone scintigraphy and indium-111 WBC imaging. *J Nucl Med.* 1988;29:1347–1353.
55. Falstie-Jensen T, Daugaard H, Søballe K, Ovesen J, Arveschoug AK, Lange J; ROSA study group. Labeled white blood cell/bone marrow single-photon emission computed tomography with computed tomography fails in diagnosing chronic periprosthetic shoulder joint infection. *J Shoulder Elbow Surg.* 2019;28:1040–1048.
56. Falstie-Jensen T, Lange J, Daugaard H, et al.; ROSA study-group. 18F FDG-PET/CT has poor diagnostic accuracy in diagnosing shoulder PJI. *Eur J Nucl Med Mol Imaging.* 2019;46:2013–2022.
57. Perno JR, Gordon A, Roach N. Osteomyelitis. In: *Radiology Secrets Plus*. 3rd ed. Philadelphia, PA: Mosby Elsevier; 2010:283–290.
58. George J, Chandy VJ, Premnath J, et al. Microbiological profile of septic arthritis in adults: lessons learnt and treatment strategies. *Indian J Med Microbiol.* 2019;37:29–33.
59. Gupta MN, Sturrock RD, Field M. A prospective 2-year study of 75 patients with adult-onset septic arthritis. *Rheumatology (Oxford).* 2001;40:24–30.
60. Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis. *Acad Emerg Med.* 2011;18:781–796.
61. Till SH, Snaith ML. Assessment, investigation, and management of acute monoarthritis. *J Accid Emerg Med.* 1999;16:355–361.
62. Expert Panel on Musculoskeletal Imaging; Beaman FD, von Herrmann PF, Kransdorf MJ, et al. ACR appropriateness criteria suspected osteomyelitis, septic arthritis, or soft tissue infection (excluding spine and diabetic foot). *J Am Coll Radiol.* 2017;14:S326–S337.
63. Learch TJ. Imaging of infectious arthritis. *Semin Musculoskelet Radiol.* 2003;7:137–142.
64. Lisbona R, Rosenthall L. Observations on the sequential use of 99mTc-phosphate complex and 67Ga imaging in osteomyelitis, cellulitis, and septic arthritis. *Radiology.* 1977;123:123–129.
65. Mudun A, Unal S, Aktay R, Akmehmet S, Cantez S. Tc-99m nanocolloid and Tc-99m MDP three-phase bone imaging in osteomyelitis and septic arthritis: a comparative study. *Clin Nucl Med.* 1995;20:772–778.
66. Coleman RE, Samuelson Jr CO, Baim S, Christian PE, Ward JR. Imaging with Tc-99m MDP and Ga-67 citrate in patients with rheumatoid arthritis and suspected septic arthritis: concise communication. *J Nucl Med.* 1982;23:479–482.
67. Devillers A, Moisan A, Jean S, Arvieux C, Bourguet P. Technetium-99m hexamethylpropylene amine oxime leucocyte scintigraphy for the diagnosis of bone and joint infections: a retrospective study in 116 patients. *Eur J Nucl Med.* 1995;22:302–307.
68. Love C, Palestro CJ. Altered biodistribution and incidental findings on gallium and labeled leukocyte/bone marrow scans. *Semin Nucl Med.* 2010;40:271–282.
69. Bruijnen ST, Gent YY, Voskuyl AE, Hoekstra OS, van der Laken CJ. Present role of positron emission tomography in the diagnosis and monitoring of peripheral inflammatory arthritis: a systematic review. *Arthritis Care Res (Hoboken).* 2014;66:120–130.