BENEFITS AND HARMS OF IMPLEMENTING THE AUC GUIDANCE

As with any appropriate use or appropriateness criteria, this document provides guidance on the potential role of testing for specific scenarios or patient presentations. Although it is meant to outline the committee's distillation and expert opinion regarding the use of nuclear medicine in these scenarios, it cannot address all patients or all clinical scenarios. Rather, it may provide support for considered clinical judgment on the basis of the available or prevailing evidence related to the use of nuclear medicine techniques in the evaluation of musculoskeletal infections.

The committee also notes that this particular topic encompasses a variety of nuclear medicine techniques and radiopharmaceuticals—bone-seeking agents, labeled leukocytes and radiolabeled glucose, and single- versus coincidence-photon based detection with and without anatomic correlation. As this document is not confined to a single target or technique, the committee hopes that it may provide clinicians with scientifically based flexibility in their approach to a clinical question. At the same time, the committee notes that the integration and complementary use of molecular/nuclear and morphological techniques may indeed provide the most appropriate strategy for what are often complex questions of infection extent and severity in the musculoskeletal system.

QUALIFYING STATEMENTS

Study/Evidence Limitations

Although the medical community has, for decades, relied on nuclear medicine imaging to evaluate musculoskeletal infection, the workgroup found that, when rigorous inclusion criteria were applied to the systematic literature review, the body of medical literature supporting the use of these procedures is limited. Investigations that initially validated these techniques do not meet the methodological standards that have been developed as the medical literature has evolved. The quality of all 10 systematic reviews included in the literature search was fair. The authors of these reviews conducted adequate literature searches, duplicate study selection and data abstraction, assessment for risk of bias, and meta-analyses. They also reported methodological limitations in their assessments of the quality of diagnostic accuracy studies. Few of them, however, reported potential conflicts of interest in the studies included in the reviews, provided details of excluded studies, or assessed for publication bias. Additional shortcomings included failure to adequately incorporate considerations of study quality when synthesizing evidence and inadequate investigations for potential sources of heterogeneity (*6*).

In the absence of available data in the systematic reviews, the workgroup conducted its own literature searches, combining the results of these searches with expert opinion when necessary in order to make recommendations about procedure appropriateness.

SPECT combined with CT has been available for nearly 2 decades. A significant advantage of SPECT/CT over planar imaging and planar plus SPECT imaging is more precise localization and characterization of foci of radiopharmaceutical uptake. This in turn results in improved specificity and diagnostic accuracy, which is associated with greater diagnostic confidence and better inter-specialty communication. SPECT/CT optimizes the diagnosis of clinically suspected musculoskeletal infection and improves the localization of known abnormalities. This is especially useful when soft tissue infection is present and the likelihood of bone involvement has to be determined. SPECT/CT is also useful for assessing the extent of infection in a complicated anatomic region, for example, in postsurgical alterations or close to implanted medical devices (*70*).

Although only 3 investigations in the systematic review included the role of SPECT/CT, all of them support its use in musculoskeletal infection (*71–73*). One study evaluated 3-phase bone scintigraphy plus SPECT and SPECT/CT in 31 patients with suspected osteomyelitis at various sites. The sensitivity of planar scintigraphy, SPECT, and SPECT/CT was the same (78%), but the specificity was higher with SPECT/CT (90%) than with SPECT (73%). The authors concluded that SPECT/CT improves the diagnostic performance of 3-phase bone scintigraphy for osteomyelitis by avoiding false-positive and equivocal results (*71*).

In an investigation of ^{99m}Tc-HMPAO-labeled leukocytes for diagnosing diabetic foot osteomyelitis, SPECT/CT changed the interpretation of planar and SPECT images in 10 of 19 suspected sites (52.6%), excluding osteomyelitis in 6 cases, revealing bone osteomyelitis in 1 case, and identifying osteomyelitis plus soft tissue infection in 3 cases (*72*).

The diagnostic accuracy of ^{99m}Tc-HMPAO-labeled leukocyte scintigraphy without SPECT versus with SPECT or with SPECT/CT for diagnosing lower extremity PJIs was studied in 164 patients. Sensitivity was 73% for scintigraphy without SPECT, 81% with SPECT, and 88% with SPECT/CT. Specificity was 93% for scintigraphy alone and with SPECT and 100% with SPECT/CT (*73*).

Two other investigations, which were not in the systematic review but were cited by the workgroup, also confirm the value of SPECT/CT in musculoskeletal infection (*16,37*). One group of investigators reported that, in patients suspected of having spondylodiscitis, ^{67}Ga SPECT/CT was superior to planar imaging for delineating the extent

of infection, especially when there was soft tissue involvement (*16*). Another study assessed combined dual-isotope SPECT/CT by using ^{111}In-labeled leukocytes, bone scintigraphy, and, when necessary, bone marrow scintigraphy in diabetic patients with foot infections and reported that SPECT/CT was more accurate than planar and SPECT imaging for diagnosing osteomyelitis (*37*).

PET/MRI combines the exquisite structural and functional characterization of tissue provided by MRI with the quantitative physiological information that is provided by PET. As exciting as its potential is, the role of PET/MRI for diagnosing infection in general, and musculoskeletal infection specifically, is still in its infancy and it is not possible at this time to make any recommendations about indications for its use.

In addition to diagnostic accuracy, an important measure of the value of a test is its effect on clinical outcomes or clinical decision making such as type of therapy and subsequent tests. Unfortunately, there were few data on the effects of nuclear medicine imaging on clinical outcomes or clinical decision making in musculoskeletal infections. One study of fair quality classified the clinical utility of ^{111}In-labeled leukocyte scintigraphy, in terms of diagnosis and/or management, as “definite” or “possible” in persons with suspected infections of various types, including 50 individuals with suspected osteomyelitis. These investigators concluded that the test definitely contributed to clinical utility in 30 of the 50 (60%) patients with suspected osteomyelitis (*74*).

One poor-quality study evaluated the proportion of patients (n = 29) in whom ^{18}F-FDG PET was associated with a “strong impact,” which was defined as new information that affected patient management (*75*). The results of ^{18}F-FDG PET led to a biopsy site change in 10% of patients and surgical intervention in 6.9%, and it extended the duration of treatment in 34% of patients.

Radiation Dose Considerations

All of the imaging procedures included in this document have been approved by the U.S. Food and Drug Administration and are therefore deemed safe and effective. Nonetheless, it is worth pointing out that there are some relative differences in radiation exposure. The ALARA principle, as low as reasonably achievable, as it pertains to radiation exposure, may be at least in part helpful in decision making about imaging protocols to answer the clinical question. Table 9 shows the relative effective dose for recommended administered activities.

TABLE 9

Radiation Doses for Nuclear Medicine Musculoskeletal Infection Imaging Procedures

	Adult administered activity		Critical organ dose		Effective dose		Reference
Radiopharmaceutical	MBq	mCi	mGy/MBq	Rad/mCi	mSv/MBq	rem/mCi	
^{18}F-FDG	370–740	10–20	0.13 (urinary bladder)	0.48	0.019	0.070	(*76*)
^{67}Ga-citrate	150–220	4.6	0.2 (lower large intestine)	0.74	0.12	0.44	(*77*)
^{111}In-oxine white blood cells (WBCs)	10–18.5	0.3–0.5	5.5 (spleen)	20	0.59	2.2	(*78*)
^{99m}Tc-HMPAO WBCs	185–370	5–10	0.15 (spleen)	0.56	0.017	0.054	(*79*)
^{99m}Tc-MDP or ^{99m}Tc-HDP	500–1110	13.5–30	0.047 (urinary bladder)		0.0049		(*80*)
^{99m}Tc-sulfur colloid	300–370	8–10	0.077 (spleen)	0.28	0.014	0.052	(*78*)

Considerations for Pregnant and Breastfeeding Patients

In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of performing the procedure. There are a variety of nuclear medicine imaging studies discussed in this guidance, some of which may have a greater radiation dose than others, as discussed earlier. Attention to procedure standards for best practices in recommendations about breastfeeding is important.

IMPLEMENTATION OF THE AUC GUIDANCE

To develop broad-based multidisciplinary clinical guidance documents, the SNMMI has been working with several other medical specialty societies. It is hoped that this collaboration will foster the acceptance and adoption of this guidance by other

specialties. SNMMI has developed a multipronged approach to disseminate AUC for musculoskeletal infection imaging to all relevant stakeholders, including referring physicians, nuclear medicine physicians, and patients. The dissemination and implementation tactics will include a mix of outreach and educational activities targeted to each of these audiences. The SNMMI will create case studies for its members, as well as for referring physicians, and make them available via online modules and webinars. These cases will cover the appropriate clinical scenarios for the use of musculoskeletal infection imaging studies. Related resources such as the systematic review supporting the development of these AUC, a list of upcoming education events on the AUC, factsheets, and other didactic materials will be made available on the SNMMI website. Live sessions will be held at the SNMMI annual and midwinter meetings, as well as at other relevant professional society meetings of referring physicians to highlight the importance and application of these AUC. SNMMI also aims to create a mobile application for these AUC for both Apple and Android platforms.

ACKNOWLEDGMENTS (Staff)

The workgroup acknowledges staff support from the Pacific Northwest Evidence-Based Practice Center of Oregon Health and Science University (Roger Chou, MD, FACP – Principal Investigator; Rebecca Jungbauer, DrPH - Research Associate; Tamara P. Cheney, MD – Research Associate; Chandler Weeks, BS – Research Assistant; Miranda Pappas, MA – Research Associate and Project Manager; Tracy Dana, MLS – Research Librarian; Elaine Graham, MLS – EPC Operations Manager provided project oversight).

APPENDIX A: WORKGROUP MEMBERS AND EXTERNAL REVIEWERS (Staff)

Workgroup

The members of the workgroup are Christopher J. Palestro, MD (chair), FSNMMI, FACNM, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY (SNMMI); Alicia Clark, MD, Beth Israel Deaconess Medical Center, Boston, MA; Erin E. Grady, MD, FACNM, Emory University School of Medicine, Atlanta, GA (ACNM, SNMMI); Sherif Heiba, MD, Mount Sinai Medical Center, New York, NY (SNMMI); Ora Israel, MD, FSNMMI, Rambam Health Care Center, Haifa, Israel (SNMMI); Alan Klitzke, MD, Roswell Park Cancer Institute, Buffalo, NY (ACNM, SNMMI); Charito Love, MD, Albert Einstein College of Medicine, Levittown, NY (SNMMI); Mike Sathekge, MD, PhD, University of Pretoria, Pretoria, South Africa (SNMMI);

Ted Treves, MD, Harvard Medical School, Boston, MA (SNMMI); Tracy L. Yarbrough, MD, PhD, California Northstate University College of Medicine, Elk Grove, CA (ACNM, SNMMI).

External Reviewers (Staff)

The external (peer) reviewers are Jamshed Bomanji, MD, PhD, Institute of Nuclear Medicine, University College London Hospitals, NHS Foundation Trust, London NW1 2BU, ENGLAND; John Buscombe, MD, FRCP, Addenbrookes Hospital, London EC1, UNITED KINGDOM; Francois Jamar, MD, PhD, Universite Catholique De Louvain Nuclear Medicine, Brussels, BELGIUM; Mathew L. Thakur, PhD, FSNMMI, Thomas Jefferson University, Philadelphia, PA; Gad S. Abikhzer, MDCM, FRCPC, ABNM, Jewish General Hospital, Montreal, QC, CANADA; Lionel S. Zukier, MD, MBA, FRCPC, Montefiore Hospital, Bronx, NY.

SNMMI (Staff)

The supporting staff from SNMMI include Sukhjeet Ahuja, MD, MPH, director, Health Policy & Quality Department, and Julie Kauffman, program manager, Health Policy & Quality Department.

APPENDIX B: DEFINITIONS OF TERMS AND ACRONYMS

ACNM: American College of Nuclear Medicine

AMSTAR: A Measurement Tool to Assess systematic Reviews

AUC: appropriate use criteria

Bone marrow scintigraphy: a diagnostic imaging test in which a radiopharmaceutical (e.g., technetium-99m [^{99m}Tc]-sulfur colloid) accumulates in the reticuloendothelial system, including normal bone marrow, and emits activity that is detected by a gamma camera. The resulting 2- or 3-dimensional images can reveal sites of absent uptake, which reflect bone marrow replacement. In suspected musculoskeletal infection, bone marrow scintigraphy is typically correlated with labeled leukocyte scintigraphy (discussed separately) to facilitate the diagnosis of osteomyelitis.

Bone scintigraphy: a diagnostic imaging test in which a radiopharmaceutical (e.g., ^{99m}Tc-methylene diphosphonate [MDP] or ^{99m}Tc-hydroxymethylene diphosphonate [HDP]) accumulates predominantly in the bones and emits activity that is detected by a gamma camera. The resulting 2- or 3-dimensional images can reveal various processes, such as bony fractures, infection,

inflammation, and changes secondary to the presence of cancer cells. Bone scintigraphy refers to planar imaging unless otherwise specified.

CI: confidence interval

COI: conflict of interest

Combined bone/^{67}Ga scintigraphy: refers to combined diagnostic imaging tests in which bone scintigraphy is performed in conjunction with ^{67}Ga-citrate scintigraphy. Imaging is usually performed in tandem and can be performed in 2 or 3 dimensions.

Combined labeled leukocyte/bone marrow scintigraphy: refers to combined diagnostic imaging tests in which radiolabeled leukocytes are imaged in conjunction with bone marrow scintigraphy. Imaging can be performed simultaneously with indium-111 (^{111}In)-oxine-labeled leukocytes by using a dual-energy approach, or in tandem if using ^{99m}Tc-hexamethylpropylene amine oxime (HMPAO)-labeled leukocytes. Imaging can be performed in 2 or 3 dimensions.

CT: computed tomography radiography, in which a 3-dimensional image of a body structure is constructed by computer from a series of planar cross-sectional images acquired along an axis.

^{18}F-FDG: ^{18}F-fluorodeoxyglucose, also referred to as fluorine-18 FDG or F-18 FDG, a frequently used radiotracer in positron emission tomography (PET) scanning. ^{18}F-FDG is a compound in which the radioactive isotope ^{18}F is attached to a molecule of glucose. Once in the body, ^{18}F-FDG is absorbed by various tissues and can be detected by a PET scanner. The resulting images show how the radiotracer is distributed within the body, helping physicians diagnose various medical conditions and assess how well the body is functioning.

^{67}Ga scintigraphy: a diagnostic imaging test in which ^{67}Ga-citrate accumulates in infectious, inflammatory, or certain types of cancerous lesions and emits activity that is detected by a gamma camera. Imaging can be acquired in 2 or 3 dimensions.

Labeled leukocyte scintigraphy: a diagnostic imaging test in which autologous leukocytes are radiolabeled with either ^{99m}Tc-HMPAO or ^{111}In-oxine. These labeled leukocytes are then reinfused into patients and accumulate in infectious or inflammatory processes and emit activity that is detected by a gamma camera. Imaging can be acquired in 2 or 3 dimensions.

HIV: human immunodeficiency virus

IV: intravenous

MRI: magnetic resonance imaging

Osteomyelitis: an infectious process of the bone caused by bacteria, viruses, and fungi, which can arise either hematogenously or via direct or contiguous inoculation. Complicated osteomyelitis is used to describe those situations in which infection develops in previously violated bone, such as tumors, fractures, and orthopedic hardware.

PET: positron emission tomography, which involves an imaging device and injection of a radiopharmaceutical into a patient's bloodstream. A frequently used PET radiopharmaceutical is ^{18}F-FDG, which the body treats like glucose. It usually takes between 30 and 60 min for the distribution of ^{18}F-FDG throughout the body to become fixed.

PET/CT: a combination, or hybrid, device that provides detail on both function and anatomy by superimposing the precise location of abnormal metabolic activity from PET on a detailed anatomic image from computed tomography (CT).

PICOTS: population, intervention, comparisons, outcomes, timing, and setting. The PICOTS format is a helpful approach to summarizing research questions that explore the effects of therapy. Population refers to the sample of subjects to be recruited for a study. There may be a fine balance between defining the sample that is most likely to respond to an intervention (e.g., no comorbidity) and the sample that can be generalized to patients likely to be seen in actual practice. Intervention refers to the treatment to be provided. Comparisons refer to a reference group. The outcomes of the reference group (no intervention applied) are compared with the outcomes of the population to which the intervention was applied. Outcomes refer to a measurement that will determine the effectiveness of the intervention. Familiar and validated outcome measurement tools relevant to common patient populations include the Neck Disability Index and the Roland-Morris Questionnaire. There are typically a multitude of outcome tools available for different clinical populations, each having strengths and weaknesses. Timing describes the duration of data collection, and setting describes the study location and its characteristics.

PJI: periprosthetic joint infection

QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies, version 2. The QUADAS tool was first developed in 2003. Experience, anecdotal reports, and feedback suggested areas for improvement, leading to QUADAS-2. The tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concern about applicability. Signaling questions are included to help judge risk of bias. The tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability. The tool allows for a more transparent rating of bias and of the applicability of primary diagnostic accuracy studies.

Septic arthritis: also termed joint infection or infectious arthritis, this is the invasion of a joint and synovial fluid by an infectious agent, resulting in joint inflammation.

SNMMI: Society of Nuclear Medicine and Molecular Imaging

SPECT: single-photon emission computed tomography, which involves injection of a radiopharmaceutical and detection by a gamma camera. The camera rotates over a 360° arc around the patient, allowing reconstruction of an image in 3 dimensions.

SPECT/CT: a combination device that provides detail on both function and anatomy by superimposing the precise location of abnormal metabolic activity from SPECT on a detailed anatomic image from CT.

Spondylodiscitis: also termed spinal or vertebral osteomyelitis or septic discitis, this is an infection of the vertebral body and/or disc.

^{99m}Tc-MDP or ^{99m}Tc-HDP: diphosphonate-based radiopharmaceuticals labeled with technetium-99m. MDP stands for methylene diphosphonate and HDP for hydroxymethylene diphosphonate (sometimes referred to as HMDP).

^{99m}Tc-sulfur colloid: the radiopharmaceutical used in bone marrow imaging.

APPENDIX C: DISCLOSURES AND CONFLICTS OF INTEREST (COIs)

The SNMMI rigorously attempted to avoid any actual, perceived, or potential COIs that might have arisen as a result of an outside relationship or personal interest on the part of the workgroup members or external reviewers. Workgroup members were required to provide disclosure statements of all relationships that might be perceived as real or potential COIs. These statements were reviewed and discussed by the workgroup chair and SNMMI staff and were updated and reviewed by an objective third party at the beginning of every workgroup meeting or teleconference. The disclosures of the workgroup members can be found in Table 10. A COI was defined as a relationship with industry—including consulting, speaking, research, and nonresearch activities—that exceeds $5,000 in funding over the previous or upcoming 12-month period. In addition, if an external reviewer was either the principal investigator of a study or another key member of the study personnel, that person's participation in the review was considered likely to present a COI. All reviewers were asked about any potential COI. A COI was also considered likely if an external reviewer or workgroup member was either the principal investigator or a key member of a study directly related to the content of this AUC document. All external reviewers were asked about any potential COI.

TABLE 10

Relationships with Industry and Other Entities

Workgroup member	Reported relationships
Clark, Alicia	• None
Grady, Erin	• None
Heiba, Sherif	• None
Israel, Ora	• General Electric, Consultant
Klitzke, Alan	• None
Love, Charito	• None
Palestro, Christopher	• None
Sathekge, Mike	• South African Medical Research Council, MIV Research, MIV/1B
Treves, Ted	• None
Yarbrough, Tracy	• Global Advanced Imaging, PLLC, Co-Owner/Staff Physician • Global CT and PET, LLC, Advisor

APPENDIX D: PUBLIC COMMENTARY (Staff)

The workgroup solicited information from all communities through the SNMMI website and through direct solicitation of SNMMI members. The comments and input helped to shape the development of these AUC on the use of nuclear medicine in musculoskeletal infection imaging.

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