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Serial X-Ray Radiography for the Diagnosis of Osteomyelitis: A Review of Diagnostic Accuracy, Clinical Utility, Cost-Effectiveness, and Guidelines

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Abbreviations

CT	Computed tomography
DFI	Diabetic foot infection
EANM	European Association of Nuclear Medicine
EBJIS	European Bone and Joint Infection Society
ESCMID	European Society of Microbiology and Infectious Disease
ESR	European Society of Radiology
IDSA	Infectious Diseases Society of America
MRI	Magnetic resonance imaging
NVO	Native vertebral osteomyelitis
PBI	Peripheral bone infection
PET	Positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SPECT	Single-photon emission computed tomography
UMHS	University of Michigan Health System
WBC	White blood cell

Context and Policy Issues

Osteomyelitis is an inflammation of the bone due to infection caused by bacteria, commonly *Staphylococcus aureus*.[1] Bacteria can reach the bone through various means including trauma, surgery, the blood stream, extension from an adjacent soft tissue infection, or diabetic foot infection.[1] Osteomyelitis can occur at any age, although the incidence appears to peak at children under the age of five and in adults over 50 years of age.[2] It can be classified as acute or chronic, based on histopathological findings.[3] Factors associated with osteomyelitis include aging, increased prevalence of trauma, and increased prevalence of diabetic foot infection.[4]

Early detection of osteomyelitis will likely lead to more favorable outcomes.[4] Diagnosis of osteomyelitis requires a multidisciplinary approach including clinical examination, recognition and assessment of clinical symptoms, laboratory investigations and imaging tests.[4] There are various imaging modalities that have been used in the characterization and differential diagnosis of osteomyelitis, such as plain X-ray radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, positron emission tomography (PET), single-photon emission computed tomography (SPECT), and ultrasonography.[1,4] The diagnostic accuracies of these imaging tests for diagnosis of osteomyelitis have been systematically reviewed.[5] Although plain X-ray radiography has lower sensitivity and specificity compared to other imaging tests, the American College of Radiology Appropriateness Criteria and reviews recommend that X-ray should be used as first line imaging modality to differentiate osteomyelitis from other clinical conditions such as bone fractures or bone malignancies.[3,6,7] Plain X-ray radiography, whether or not with positive or negative results, is usually followed by higher sensitivity and specificity imaging modalities for diagnosis of osteomyelitis.[8] However, in institutions where the availability of more sophisticated imaging modalities is limited, it is unclear if the use of serial X-ray radiography (i.e., initial assessment with X-rays followed by subsequent X-rays in 1 to 3 weeks), could improve diagnostic accuracy for detection of osteomyelitis.

The aim of this report is to review the diagnostic accuracy, clinical utility, and cost-effectiveness of serial X-ray radiography in adults with suspected osteomyelitis compared

to other diagnostic modalities. This report also aims to identify evidence-based guidelines regarding the use of diagnostic modalities in adults with suspected osteomyelitis.

Research Question

1. What is the diagnostic accuracy of serial X-ray radiography in adults with suspected osteomyelitis?
2. What is the clinical utility of serial X-ray radiography in adults with suspected osteomyelitis?
3. What is the cost-effectiveness of serial X-ray radiography in adults with suspected osteomyelitis?
4. What are the evidence-based guidelines regarding the use of diagnostic modalities in adults with suspected osteomyelitis?

Key Findings

This review included three evidence-based guidelines for diagnosis of peripheral bone infection, diabetic foot infection, and native vertebral osteomyelitis in adults. No studies on the diagnostic accuracy, clinical utility and cost-effectiveness of serial X-ray radiography for diagnosis of osteomyelitis were identified.

All three guidelines were considered to be of good methodological quality. Based on moderate to low quality evidence, the guidelines had recommendations for diagnosis of osteomyelitis regarding medical examination, laboratory tests, bone biopsy and bone culture, and imaging tests. Bone biopsy and bone culture are considered as the reference standard to confirm the infection and identify the causative microorganism. Although magnetic resonance imaging, positron emission tomography and single-photon emission computed tomography were found to have higher diagnostic performance than radiography, it is recommended that conventional X-ray radiography should be the first imaging modality for detection of osteomyelitis, particularly for suspected peripheral bone infection or for osteomyelitis in diabetic foot infection. With suspected native vertebral osteomyelitis, spine magnetic resonance imaging, when feasible, is recommended as first imaging of choice. Subsequent imaging tests may be considered depending on the extent of the investigation, the availability of the imaging modalities, the level of diagnostic accuracy required, the complexity of the disease, and any contraindications.

There is a need for studies examining the diagnostic accuracy, clinical utility and cost-effectiveness of serial X-ray radiography for detection of osteomyelitis in adults.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were x-ray

radiography and osteomyelitis. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and February 14, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with suspected osteomyelitis (acute or chronic, with or without diabetic foot ulcer)
Intervention	Q1-Q3: Serial X-ray radiography Q4: Any diagnostic modalities (e.g., imaging modalities, laboratory tests, clinical assessment)
Comparator	Q1: Reference standard: histologic or microbiologic results of surgical biopsy specimens or any alternative diagnostic modalities (e.g., computed tomography, leukocyte scintigraphy, magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, technetium-99 bone scintigraphy, gallium scans, clinical assessment) Q2-Q3: Alternative diagnostic modalities (e.g., computed tomography, leukocyte scintigraphy, magnetic resonance imaging, positron emission tomography, single-photon emission computed tomography, technetium-99 bone scintigraphy, gallium scans, clinical assessment) Q4: No comparator required
Outcomes	Q1: Diagnostic accuracy (e.g., sensitivity, specificity, true positive rate, false positive rate) Q2: Clinical utility (e.g., mortality, morbidity, amputations, prevention of severe infection) Q3: Cost-effectiveness Q4: Recommendations regarding best practices (e.g., diagnostic pathways or protocols)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 or if they were published prior to 2015.

Critical Appraisal of Individual Studies

The included evidence-based guidelines were critically appraised using the Appraisal of Guidelines for Research and Development (AGREE) II instrument.[9] Summary scores were not calculated for the included guidelines; rather, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 662 citations were identified in the literature search. Following screening of titles and abstracts, 641 citations were excluded and 21 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications

were retrieved from the grey literature search. Of the 23 potentially relevant articles, 20 publications were excluded for various reasons; three guidelines met the inclusion criteria and were included in this report. No studies reporting the diagnostic accuracy, clinical utility, or cost-effectiveness of serial X-ray radiography in adults with suspected osteomyelitis were identified. Appendix 1 presents the PRISMA flowchart[10] of the study selection.

Summary of Study Characteristics

The detailed characteristics of the included guidelines[11-13] (Table 2) are presented in Appendix 2.

Study Design

The included guidelines were developed by: four European societies (European Bone and Joint Infection Society [EBJIS], European Society of Clinical Microbiology and Infectious Diseases [ESCMID], European Society of Radiology [ESR], and European Association of Nuclear Medicine [EANM]),[11] the University of Michigan Health System (UMHS),[12] and the Infectious Diseases Society of America (IDSA).[13] All three included guidelines[11-13] used systematic methods to search for, select, and synthesize evidence. The guidelines were developed by panels of experts in the field of osteomyelitis in general, or diabetic foot infection in particular. The recommendations were developed through discussion and consensus based on evidence level. The joint consensus statements in the EBJIS/ESCMID/ESR/EANM European guideline[11] were rated with the associated level evidence, where level 1 represented for evidence from systematic reviews of randomized trials and level 5 from mechanism-based reasoning. In the UMHS guideline,[12] the strength of recommendation (e.g., I = generally should be performed, II = may be reasonable to performed, and III = generally should not be performed) and level of evidence (level A = systematic reviews of randomized trials with or without meta-analysis, to level E = expert opinion) were provided for each recommendation statements. In the IDSA guideline,[13] the recommendations were graded from strong to weak, while the quality of evidence was assessed as high quality to very low quality. The strength of recommendation and the quality of the evidence were presented together based on the clarity of balance between desirable and undesirable effects, the methodological quality of supporting evidence and implications of recommendations.[13] All guidelines were peer-reviewed. Two guidelines were published in 2019[11,12] and one in 2015.[13]

Country of Origin

One guideline was developed in Europe,[11] and two in the USA.[12,13]

Patient Population

The target populations for the identified guidelines was adult patients with a suspicion of peripheral bone infection,[11] with diabetic foot infection,[12] or with native vertebral osteomyelitis.[13] The intended users of the guidelines were healthcare professionals.

Interventions and Comparators

The interventions considered in the guidelines were interventions for the diagnosis and management of adult patients with peripheral bone infection,[11] diabetic foot infection,[12] and native vertebral osteomyelitis.[13] Imaging modalities mentioned in the guidelines included plain X-ray radiography, CT, MRI, PET, SPECT and scintigraphy. Serial X-ray radiography was not mentioned in any of the included guidelines.

Outcomes

All included guidelines had recommendations regarding the diagnosis of osteomyelitis, specifically peripheral bone infection,[11] diabetic foot infections,[12] or native vertebral osteomyelitis[13] in adults. The guidelines considered all outcomes related to diagnosis and management of osteomyelitis, including clinical assessment, symptoms, signs, laboratory parameters, bone biopsy, and imaging tests. In addition to diagnostic outcomes, the availability of diagnostic procedures, patient acceptance, tolerability, complications, and costs were considered in developing the recommendations.

Summary of Critical Appraisal

The detailed quality assessments of the included guidelines[11-13] (Table 3) are presented in Appendix 3.

All three included guidelines[11-13] were explicit in terms of scope and purpose (i.e., objectives, health questions and populations), and had clear presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, the guidelines clearly defined target users and the development groups included individuals from all relevant professional groups, and sought the views and preferences of the target populations. For rigour of development, the guidelines explicitly reported details of systematic searches for evidence, criteria for selecting evidence, strengths and limitations of the body of evidence, methods of formulating the recommendations, health benefits, side effects, and risks in formulating the recommendations, and all were peer-reviewed prior to publication. Two guidelines[11,12] provided a procedure for updating. For applicability, all guidelines were explicit in terms of facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, resource (cost) implications, and monitoring and or auditing criteria. For editorial independence, it was unclear if the funding bodies influenced the content of the guidelines. The EBJIS/ESCMID/ESR/EANM European guideline[11] did not mention its funding source, the UMHS guideline[12] declared no financial support, and the IDSA guideline[13] was funded its own organization. The competing interests of guideline development group members were reported in all three guidelines. Overall, all three included guidelines had good methodological quality.

Summary of Findings

Diagnostic Accuracy of Serial X-Ray Radiography

No studies regarding the diagnostic accuracy of serial X-ray radiography in adults with suspected osteomyelitis were identified; therefore, no summary can be provided.

Clinical Utility of Serial X-Ray Radiography

No studies regarding the clinical utility of serial X-ray radiography in adults with suspected osteomyelitis were identified; therefore, no summary can be provided.

Cost-Effectiveness of Serial X-Ray Radiography

No studies regarding the cost-effectiveness of serial X-ray radiography in adults with suspected osteomyelitis were identified; therefore, no summary can be provided.

Guidelines Regarding the Use of Diagnostic Modalities in Detecting Osteomyelitis in Adults

The key recommendations of the guidelines[11-13] (Table 4) are presented in Appendix 4.

The joint EBJIS/ESCMID/ESR/EANM guideline provided recommendations specific to patients with suspected peripheral bone infection.[11] The guideline[11] recommends laboratory tests of C-reactive protein, erythrocyte sedimentation rate, and white blood cell count be performed in patients with suspected peripheral bone infection for diagnosis purposes (*Level of evidence: 4*). The guideline recommends conventional X-ray radiography to be used as first imaging modality for diagnosis and follow-up of suspected peripheral bone infection (*Level of evidence: 3*). Once peripheral bone infection is diagnosed by clinical and radiological means, bone biopsy is the reference standard to confirm the infection and should be conducted to identify the microorganism causing the infection (*Level of evidence: 4*). In complex anatomic areas, CT is recommended as an adjunct imaging modality to the conventional radiographs to detect bone sequestra (*Level of evidence: 4*). The guideline acknowledges that non-contrast MRI has high diagnostic performance (*Level of evidence: 2*), three-phase bone scintigraphy is sensitive, but not highly specific (*Level of evidence: 2*), and white blood cell scintigraphy and antigranulocyte antibody scintigraphy have similar diagnostic accuracy (*Level of evidence: 2*) in diagnosis of peripheral bone infection. The guideline also acknowledges that PET has high diagnostic accuracy in diagnosis of peripheral bone infection without fracture and osteosynthesis (*Level of evidence: 2*). No specific recommendations were provided for these diagnostic modalities. The guideline suggests that the use of hybrid SPECT-CT imaging can improve the detection of exact localization of infection (*Level of evidence: 2*). When hematogenous spread of the infection is suspected, the guideline recommends PET/CT to be used as the first imaging modality (*Level of evidence: 5*).

The UMHS guideline[12] provided recommendations specific to patients with diabetic foot infection. It recommends bone biopsy and bone culture for suspected osteomyelitis in diabetic foot infections (*Strength of recommendation: I; Level of evidence: C*). For imaging tests, the guideline recommends that X-ray radiography is used firstly to evaluate suspected non-superficial soft tissue infection or osteomyelitis (*Strength of recommendation: I; Level of evidence: C*). With suspected soft tissue abscess, MRI is recommended as the next imaging test (*Strength of recommendation: II; Level of evidence: E*). In case if negative or equivocal radiograph of suspected osteomyelitis, or if there is a need to evaluate the extent of osteomyelitis on positive radiograph, the guideline recommends MRI as the next imaging test (*Strength of recommendation: I; Level of evidence: C*). If MRI is not available, the guideline recommends the use of triple-phase bone scan in combination with tagged white blood cell scan (*Strength of recommendation: I; Level of evidence: C*).

The IDSA guideline[13] provided recommendations specific to patients with suspected native vertebral osteomyelitis. It recommends a medical and neurological examination, as well as laboratory tests including bacterial (aerobic and anaerobic) blood cultures, baseline erythrocyte sedimentation rate and C-reactive protein in patients with suspected native vertebral osteomyelitis (*Strong recommendation; Low-quality evidence*). The guideline recommends spine MRI in patients with suspected native vertebral osteomyelitis (*Strong recommendation; Low-quality evidence*). When MRI is not available or cannot be obtained in patients having implantable cardiac devices, cochlear implants, or claustrophobia, the guideline suggests the use of a combination of spine gallium/Tc99 bone scan, or a CT scan, or a PET scan (*Weak recommendation; Low-quality evidence*). In patients with

subacute native vertebral osteomyelitis who are living in endemic area for brucellosis, the guideline recommends performing blood cultures and serologic tests for *Brucella* species (*Strong recommendation; Low-quality evidence*). Performing fungal blood cultures is suggested in patients with suspected native vertebral osteomyelitis and at risk of fungal infection (*Weak recommendation; Low-quality evidence*). In patients with subacute native vertebral osteomyelitis and at risk of *Mycobacterium tuberculosis*, the guideline suggests conducting a purified protein derivative test or obtaining an interferon-ɣ release assay (*Weak recommendation; Low-quality evidence*).

Limitations

There was a lack of evidence regarding the diagnostic accuracy of serial X-rays (i.e., initial assessment with X-rays followed by subsequent X-rays in 1 to 3 weeks) in adults with suspected osteomyelitis. Similarly, there was a lack of evidence regarding the clinical utility and cost-effectiveness of serial X-ray radiography for the detection of osteomyelitis in adults.

Conclusions and Implications for Decision or Policy Making

This review included three evidence-based guidelines for diagnosis of peripheral bone infection,[11] diabetic foot infection[12] and native vertebral osteomyelitis[13] in adults.

The included guidelines had recommendations for diagnosis of osteomyelitis at different body parts (i.e., peripheral bone infection,[11] diabetic foot infection[12] and native vertebral osteomyelitis[13]), regarding medical examinations, laboratory tests, bone biopsies and bone cultures, and imaging tests. Two guidelines[11,12] recommend X-ray radiography to be used as first-line imaging modality for the diagnosis of osteomyelitis in peripheral bone infection or in diabetic foot infection. One guideline[13] recommends spine MRI in patients with suspected native vertebral osteomyelitis, without mentioning anything about radiography. Bone biopsy and bone culture are considered as the reference standard to confirm the infection and identify the causative microorganism.[11-13] All three guidelines[11-13] had recommendations for the use other imaging modalities including MRI, CT, PET, SPECT, scintigraphy depending on the extent of the investigation, the availability of the imaging modalities, the level of diagnostic accuracy required, the complexity of the disease, and patients' contraindication.

Overall, despite MRI, PET and SPECT having been found to have higher diagnostic performance than radiography, it is recommended that conventional X-ray radiography should be the first imaging modality for detection of osteomyelitis, particularly in peripheral bone infection or in diabetic foot infection. With suspected native vertebral osteomyelitis, spine MRI, when feasible, is recommended as first imaging choice for diagnosis.

There is a need for studies examining the diagnostic accuracy, clinical utility and cost-effectiveness of serial X-ray radiography for detection of osteomyelitis in adults.

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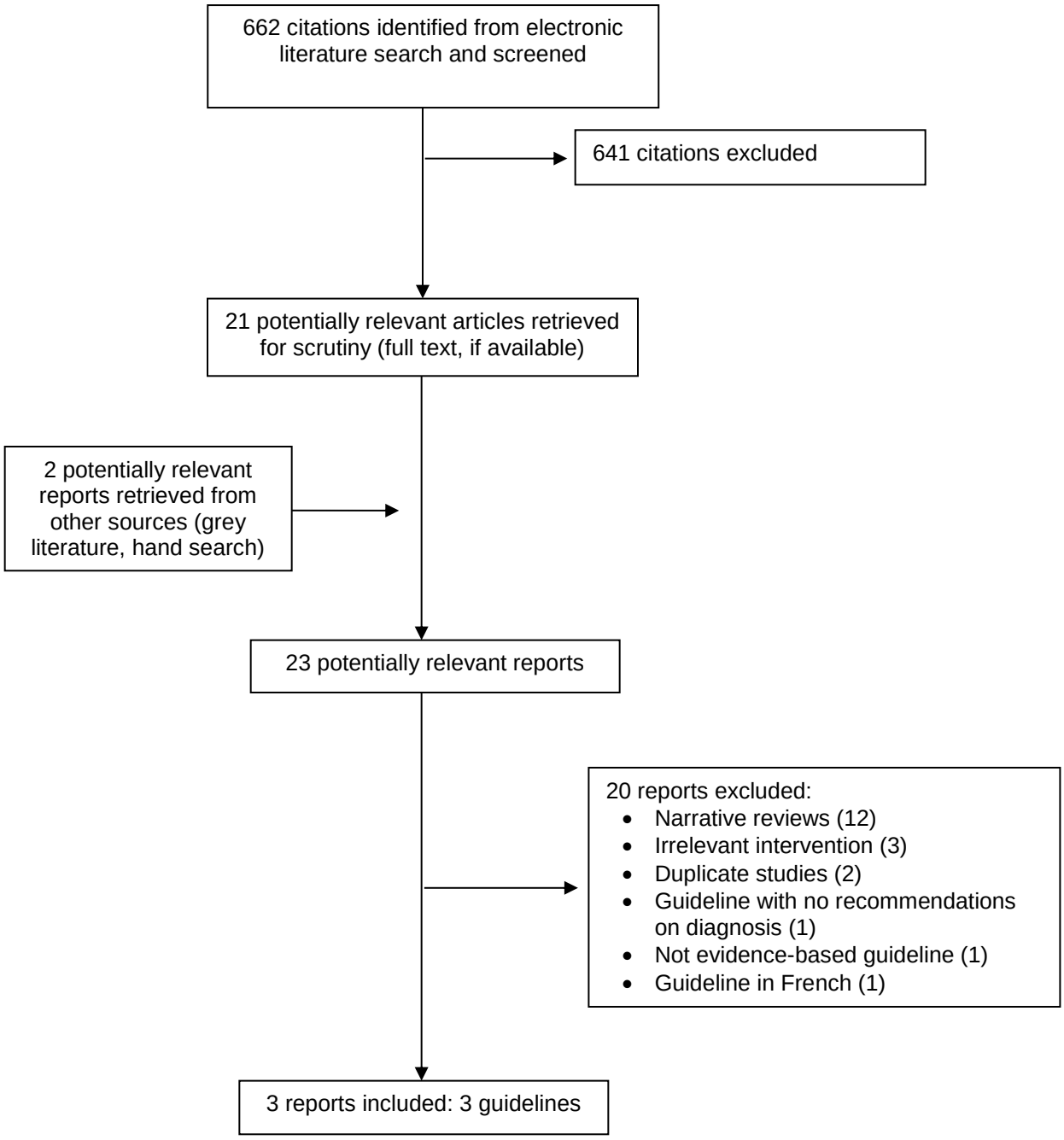
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
EANM, EBJIS, ESR, and ESCMID, Glaudemans et al., 2019[11] Europe Funding: Unclear	Intended users: Healthcare professionals Target population: Adult patients with a suspicion of peripheral bone infection (PBI)	Diagnostic management of adult patients with PBI. Diagnostic imaging modalities considered included radiography, CT, MRI, PET, SPECT and scintigraphy	All outcomes related to diagnosis of PBI (clinical assessment, symptoms, sings, laboratory parameters, bone biopsy, radiological and nuclear medicine imaging methods)	Systematic methods were used to search for evidence, selection and synthesis	The guideline was developed by members from four European societies, who defined clinical questions to be addressed, reviewed the literature and evaluated the diagnostic accuracy of each diagnostic technique. Each consensus statement was followed by a level of evidence[a] created by the Oxford Centre for Evidence-Based Medicine 2011[14]	The guideline was peer-reviewed
UMHS, Mills et al., 2019[12] USA Funding: No financial support	Intended users: All healthcare professionals involving in the care of patients with diabetic foot infection (DFI) Target population: Adult patients with DFI	Diagnostic management of adult patients with DFI. Diagnostic imaging modalities considered included radiography, MRI, and scintigraphy	All outcomes related to diagnosis, imaging and treatment of DFI	Systematic methods were used to search for evidence, selection and synthesis	The guideline was developed by team members who are experts in the field of DFI. The strength of recommendations[b] were graded based on the level of evidence[c]	The guideline was peer-reviewed
IDSA, Berbari et al., 2015[13] USA	Intended users: Infectious disease specialists, orthopedic surgeons,	Diagnosis and treatment of NVO in adults. Diagnostic imaging	All outcomes related to diagnosis, and management of NVO	Systematic methods were used to search for evidence, selection and synthesis	The guideline was developed by an expert panel.	The guideline was peer-reviewed

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
Funding: IDSA	neurosurgeons, radiologists, and other healthcare professionals who care for patients with native vertebral osteomyelitis (NVO) Target population: Adult patients with NVO	modalities considered included MRI, gallium/Tc99 bone scan, CT, and PET			The strength of recommendation and quality of evidence were systematically weighted using GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[d]	

CT = computed tomography; DFI = diabetic foot infection; EANM = European Association of Nuclear Medicine; EBJIS = European Bone and Joint Infection Society; ESCMID = European Society of Microbiology and Infectious Disease; ESR = European Society of Radiology; IDSA = Infectious Diseases Society of America; MRI = magnetic resonance imaging; NVO = native vertebral osteomyelitis; PBI = peripheral bone infection; PET = positron emission tomography; SPECT = single-photon emission computed tomography; UMHS = University of Michigan Health System.

[a] Level of evidence
Level 1: Systematic review of randomized trials
Level 2: Randomized trial
Level 3: Non-randomized controlled cohort/follow-up study
Level 4: Case-series, case-control, or historical controlled studies
Level 5: Mechanism-based reasoning

[b] Strength of recommendation:

I = Generally should be performed
II = May be reasonable to perform
III = Generally should not be performed

[c] Level of evidence:
A = systematic review of randomized controlled trials with or without meta-analysis
B = randomized controlled trials
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observational studies (cohort, cross-sectional, case-control)
D = individual observational studies (case study/case series)
E = expert opinion regarding benefits and harm

[d] Details of the strength of recommendations, quality of evidence, clarity of balance between desirable and undesirable effects, and implications are presented in the published guideline.[13] The recommendations were graded from strong to weak, while the quality of evidence was assessed as high quality to very low quality. The strength of recommendation and the quality of the evidence were presented together based on the clarity of balance between desirable and undesirable effects, the methodological quality of supporting evidence and implications of recommendations.

Appendix 3: Quality Assessment of Included Studies

Table 3: Quality Assessment of Guidelines

AGREE II checklist[9]	EANM, EBJIS, ESR, and ESCMID, Glaudemans et al., 2019[11]	UMHS, Mills et al., 2019[12]	IDSA, Berbari et al., 2015[13]
Scope and purpose	—	—	—
1. Objectives and target patient population were explicit	Yes	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes	Yes
3. The population to whom the guidelines is meant to apply is specifically described	Yes	Yes	Yes
Stakeholder involvement	—	—	—
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes	Yes
5. The views and preferences of the target population have been sought	Yes	Yes	Yes
6. The target users of the guideline are clearly defined	Yes	Yes	Yes
Rigour of development	—	—	—
7. Systematic methods were used to search for evidence	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Yes	Yes	Yes
14. A procedure for updating the guideline is provided	Yes	Yes	Unclear
Clarity of presentation	—	—	—
15. The recommendations are specific and unambiguous	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes	Yes
Applicability	—	—	—
18. The guideline describes facilitators and barriers to its application	Yes	Yes	Yes
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes	Yes	Yes

AGREE II checklist[9]	EANM, EBJIS, ESR, and ESCMID, Glaudemans et al., 2019[11]	UMHS, Mills et al., 2019[12]	IDSA, Berbari et al., 2015[13]
20. The potential resource (cost) implications of applying the recommendations have been considered	Yes	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria	Yes	Yes	Yes
Editorial independence	—	—	—
22. The views of the funding body have not influenced the content of the guideline	Unclear	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes	Yes

EANM = European Association of Nuclear Medicine; EBJIS = European Bone and Joint Infection Society; ESR = European Society of Radiology; ESCMID = European Society of Microbiology and Infectious Disease; IDSA = Infectious Diseases Society of America; UMHS = University of Michigan Health System.

Appendix 4: Recommendations in Included Guidelines

Table 4: Summary of Recommendations in Included Guidelines

Recommendations (strength of recommendations, levels of evidence)
EANM, EBJIS, ESR, and ESCMID, Glaudemans et al., 2019[11]
The strength of the following recommendations (e.g., strong or weak) was not provided. *"Statements on the diagnosis of peripheral bone infection* – *Patients presenting with clinical and radiological signs of peripheral bone infection or a positive probe-to-bone test may require further diagnostic procedures. (Level of evidence[a]: 5)* – *Fistula direct to the bone and purulent discharge are evidence of bone infection. (Level of evidence[a]: 5)* – *C-reactive protein, erythrocyte sedimentation rate, and white blood cell counts should always be performed in patients suspected to have peripheral bone infection for diagnosis purposes. (Level of evidence[a]: 4)* – *Blood cultures should be considered in patients with fever suspected to have peripheral bone infection for the diagnosis the involved bacteria. (Level of evidence[a]: 4)* – ***Conventional radiography is the first imaging modality to be performed in patients suspected of having peripheral bone infection for diagnosis and follow-up.*** *(Level of evidence[a]: 3)* – *In case of clinical and radiological signs of peripheral bone infection, bone biopsy is the reference standard for confirming infection and identifying the causative microorganism. (Level of evidence[a]: 4)* – *In case of clinical and radiological signs of peripheral bone infection, sinus tract cultures and/or superficial swab cultures should be discouraged in the diagnostic work-up; bone biopsy is the gold standard. (Level of evidence[a]: 4)* – *CT should be used as an adjunct to conventional radiographs in complex anatomic areas and is useful to detect bone sequestra. (Level of evidence[a]: 4)* – *Non-contrast MRI had high diagnostic performance in detecting peripheral bone infection. (Level of evidence[a]: 2)* – *Three-phase bone scintigraphy is a sensitive technique in patients suspected for peripheral bone infection although not highly specific. (Level of evidence[a]: 2)* – *White blood cell (WBC) scintigraphy and antigranulocyte antibody (AGA) scintigraphy have similar diagnostic accuracy for diagnosis of peripheral bone infection. (Level of evidence[a]: 2)* – *^{18}F-FDG-PET has high diagnostic accuracy in peripheral bone infection without fracture and osteosynthesis. (Level of evidence[a]: 2)* – *Hybrid SPECT-CT WBC imaging can be performed for exact localization of infection site. (Level of evidence[a]: 2)* – *When having a suspicion for hematogenous spread of the infection, ^{18}F-FDG-PET/CT is the first imaging modality of choice. (Level of evidence[a]: 5)"*[11] p. 961 to 967
UMHS, Mills et al., 2019[12]
Diabetic foot infections – *"If osteomyelitis is suspected, obtain bone culture to guide antibiotic therapy rather than soft tissue culture if clinically feasible; do not obtain superficial swab. (Strength of recommendation[b]: I; Level of evidence[c]: C)* – ***Obtain foot radiographs for initial evaluation of suspected non-superficial soft tissue infection or osteomyelitis.*** *(Strength of recommendation[b]: I; Level of evidence[c]: C)* – *Perform MRI as the next imaging test if soft tissue abscess is suspected. (Strength of recommendation[b]: II; Level of evidence[c]: E)* – *If osteomyelitis is suspected despite negative or equivocal radiograph, or if additional imaging is needed to evaluate the extend of osteomyelitis, perform an MRI as the next imaging test. (Strength of recommendation[b]: I; Level of evidence[c]: C)* – *Obtain a triple-phase bone scan in combination with tagged WBC scan if MRI cannot be obtained but further evaluation of osteomyelitis is needed. (Strength of recommendation[b]: I; Level of evidence[c]: C)"*[12] p.1
IDSA, Berbari et al., 2015[13]
"What is the appropriate diagnostic evaluation of patients with suspected NVO?

Recommendations (strength of recommendations, levels of evidence)
– *We recommend performing a pertinent medical and motor/sensory neurologic examination in patients with suspected NVO. (Strong recommendation; Low-quality evidence)*[d] – *We recommend obtaining bacterial (aerobic and anaerobic) blood cultures (2 sets) and baseline erythrocyte sedimentation rate and C-reactive protein in all patients with suspected NVO. (Strong recommendation; Low-quality evidence)*[d] – *We recommend a spine MRI in patients with suspected NVO. (Strong recommendation; Low-quality evidence)*[d] – *We suggest a combination of spine gallium/Tc99 bone scan, or computed tomography scan or a position emission tomography scan in patients with suspected NVO when MRI cannot be obtained (e.g., implantable cardiac devices, cochlear implants, claustrophobia, or unavailability). (Weak recommendation; Low-quality evidence)*[d] – *We recommend obtaining blood cultures and serologic tests for Brucella species in patients with subacute NVO residing in endemic areas for brucellosis. (Strong recommendation; Low-quality evidence)*[d] – *We suggest obtaining fungal blood cultures in patients with suspected NVO and at risk for fungal infection (epidemiology risk or host risk factors). (Weak recommendation; Low-quality evidence)*[d] – *We suggest performing a purified protein derivative (PPD) test or obtaining an interferon-γ release assay in patients with subacute NVO and at risk for Mycobacterium tuberculosis NVO (i.e., originating or residing in endemic regions or having risk factors). (Weak recommendation; Low-quality evidence)*[d] – *In patients with suspected NVO, evaluation by an infectious disease specialist and a spine surgeon may be considered. (Weak recommendation; Low-quality evidence)*[d,13] p. e27

CT = computed tomography; EANM = European Association of Nuclear Medicine; EBJIS = European Bone and Joint Infection Society; ESCMID = European Society of Microbiology and Infectious Disease; ESR = European Society of Radiology; IDSA = Infectious Diseases Society of America; MRI = magnetic resonance imaging; NVO = native vertebral osteomyelitis; PET = positron emission tomography; SPECT = single-photon emission computed tomography; UMHS = University of Michigan Health System; WBC = white blood cell.

[a] Level of evidence
Level 1: Systematic review of randomized trials
Level 2: Randomized trial
Level 3: Non-randomized controlled cohort/follow-up study
Level 4: Case-series, case-control, or historical controlled studies
Level 5: Mechanism-based reasoning

[b] Strength of recommendation:

I = Generally should be performed
II = May be reasonable to perform
III = Generally should not be performed

[c] Level of evidence:
A = systematic review of randomized controlled trials with or without meta-analysis
B = randomized controlled trials
C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observational studies (cohort, cross-sectional, case-control)
D = individual observational studies (case study/case series)
E = expert opinion regarding benefits and harm

[d] Details of the strength of recommendations, quality of evidence, clarity of balance between desirable and undesirable effects, and implications are presented in the published guideline.[13] The recommendations were graded from strong to weak, while the quality of evidence was assessed as high quality to very low quality. The strength of recommendation and the quality of the evidence were presented together based on the clarity of balance between desirable and undesirable effects, the methodological quality of supporting evidence and implications of recommendations.

Appendix 5: Additional References of Potential Interest

Allahabadi S, Haroun KB, Musher DM, Lipsky BA, Barshes NR. Consensus on surgical aspects of managing osteomyelitis in the diabetic foot. *Diabet Foot Ankle.* 2016;7:30079.