Diagnostic Accuracy of the Physical Examination and Imaging Tests for Osteomyelitis Underlying Diabetic Foot Ulcers: Meta-Analysis

Marie T. Dinh, Cybele L. Abad, and Nasia Safdar
Section of Infectious Diseases, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison

Accurate diagnosis of osteomyelitis underlying diabetic foot ulcers is essential to optimize outcomes. We undertook a meta-analysis of the accuracy of diagnostic tests for osteomyelitis in diabetic patients with foot ulcers. Pooled sensitivity and specificity, the summary measure of accuracy (Q*), and diagnostic odds ratio were calculated. Exposed bone or probe-to-bone test had a sensitivity of 0.60 and a specificity of 0.91. Plain radiography had a sensitivity of 0.54 and a specificity of 0.68. MRI had a sensitivity of 0.90 and a specificity of 0.79. Bone scan was found to have a sensitivity of 0.81 and a specificity of 0.28. Leukocyte scan was found to have a sensitivity of 0.74 and a specificity of 0.68. The diagnostic odds ratios for clinical examination, radiography, MRI, bone scan, and leukocyte scan were 49.45, 2.84, 24.36, 2.10, and 10.07, respectively. The presence of exposed bone or a positive probe-to-bone test result is moderately predictive of osteomyelitis. MRI is the most accurate imaging test for diagnosis of osteomyelitis.

Foot wounds are the most common diabetes-related reason for hospitalization and often herald the need for amputation [1, 2]. Patients with diabetes have a 10-fold greater risk of soft-tissue infection and bone infection in the lower extremity, compared with healthy individuals [3, 4]. Osteomyelitis may complicate as many as 20% of diabetic foot ulcers [5].

Diagnosis of osteomyelitis underlying a diabetic foot ulcer is challenging because of the lack of a single, noninvasive, highly sensitive and specific test. Clinical and laboratory clues are variable and often nonspecific [6, 7]. Imaging tests, such as plain radiography, provide negative results during the early stage of osteomyelitis and lack specificity when the results are positive, because other conditions, such as Charcot neuroarthropathy, may appear radiographically very similar to osteomyelitis [8–10]. We undertook a meta-analysis to critically evaluate the diagnostic accuracy of clinical examination and imaging tests for diagnosis of osteomyelitis in diabetic patients with foot ulcers.

METHODS

Literature search and selection. We searched the Medline and Cumulative Index to Nursing and Allied Health Literature databases with use of the search terms “diabetic” and “osteomyelitis” or “diabetic” and “ulcer,” in addition to each of the following words: size, depth, imaging, MRI, CT scan, nuclear scan, PET scan, plain X-ray, bone scan, and leukocyte scan. The search was limited to studies involving adults and to English-language articles from the period 1966 through 27 February 2007.

We included studies that (1) assessed the accuracy of clinical or imaging diagnostic modalities for diagnosis of osteomyelitis in individuals with diabetes and foot ulcer and (2) used histopathologic examination and/or microbiologic culture of bone specimens as the

Received 13 September 2007; accepted 9 April 2008; electronically published 7 July 2008.
Reprints or correspondence: Dr. Nasia Safdar, University of Wisconsin-Madison, Wm. S. Middleton VA Center, H4/513 CSC, 600 Highland Ave., Madison, WI 53792 (ns2@medicine.wisc.edu).
Clinical Infectious Diseases 2008;47:519–27
© 2008 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2008/4704-0013$15.00
DOI: 10.1086/590011

Diagnosis of Osteomyelitis • CID 2008:47 (15 August) • 519
reference test for diagnosis of osteomyelitis [6]. For studies that included patients with and without diabetes, only patients with diabetes were included in our analysis. For each study, all patients had to have participated in the test being studied and the reference test.

A standard form was used to extract the relevant data. The Standards for Reporting of Diagnostic Accuracy Initiative and the Review of Methodological Standards were used to assess study quality [11, 12]. A list of trials that did not meet inclusion criteria and the reasons for exclusion are available from the authors.

We reviewed 6 diagnostic methods that met appropriate quality standards. The clinical examination features included ulcer appearance, ulcer size, and the presence of exposed or palpable bone. The other diagnostic tests included plain radiography, MRI, nuclear medicine bone scan, and indium-labeled leukocyte scan. Table 1 shows commonly accepted definitions for each diagnostic method.

**Statistical analysis.** Sensitivity and specificity for clinical examination and diagnostic imaging tests were calculated from the data in each study. Pooled sensitivities and specificities were calculated for each diagnostic imaging test with use of the DerSimonian-Laird random effects model [18]; an assessment of heterogeneity was performed with use of the Cochran Q statistic. Heterogeneity refers to inconsistency stemming from differing results of the included studies [19]. For each feature of the clinical examination and diagnostic imaging tests, positive and negative likelihood ratios were calculated. A pooled diagnostic OR was calculated for each of the diagnostic tests evaluated [20]. The diagnostic OR expresses how much greater the odds of having the disease are for persons who had a positive test result, relative to people who had a negative test result. It is a single measure of diagnostic test performance that combines both likelihood ratios. The value of a diagnostic OR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A diagnostic OR of 1 means that a test does not discriminate between patients with the disorder and those without it.

We also calculated a summary measure of accuracy (Q*), which corresponds to the upper left-most point on the summary receiver operating characteristic curve where sensitivity equals specificity; Q* has been advocated over the area under the receiver operating characteristic curve, because it is useful in the receiver operating characteristic curve region of greatest interest [21, 22]. All statistical analyses were performed with use of MetaDisc software [23].

**RESULTS**

Of the initial 917 articles retrieved from the literature search, 9 studies were included in the review; 59 studies that were identified by perusing reference lists of potentially relevant articles were also included. Figure 1 illustrates the literature search process.

Study methodology was variable in the included studies. Table 2 summarizes study quality. Only 33% of the trials provided

---

**Table 1. Major diagnostic methods for diagnosing osteomyelitis associated with diabetic foot ulcer**

<table>
<thead>
<tr>
<th>Diagnostic method, references</th>
<th>Criteria for positivity</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histopathologic examination</td>
<td>Osteonecrosis and infiltration with leukocytes or chronic inflammatory cells, such as lymphocytes or plasma cells</td>
<td>[13, 14]</td>
</tr>
<tr>
<td>Ulcer measurement</td>
<td>Area was determined by multiplying the longest and widest diameters; depth was graded as very deep (exposing bone), moderately deep (&gt;3 mm, but not exposing bone), or shallow (&lt;3 mm)</td>
<td>[15]</td>
</tr>
<tr>
<td>Radiography</td>
<td>Focal or geographic areas of marrow radiolucency, loss of cortex with bony erosion, new bone formation, bone sclerosis with or without erosion, soft-tissue inflammation, sequestration, involucrum, cloaca, and periosteal elevation</td>
<td>[13, 16]</td>
</tr>
<tr>
<td>MRI</td>
<td>Decreased signal intensity on T1-weighted images with focal enhancement after contrast and increased signal intensity on T2-weighted images</td>
<td>[13, 17]</td>
</tr>
<tr>
<td>3-Phase bone scintography</td>
<td>Increased blood flow and blood-pool activity and abnormally increased intensity localized to the bone</td>
<td>[16]</td>
</tr>
<tr>
<td>Leukocyte scan</td>
<td>Focal abnormal increased activity</td>
<td>[14]</td>
</tr>
</tbody>
</table>
demographic characteristics of the sample population, including age, sex, comorbidities, and details of glycemic control. By restricting our inclusion criteria to studies that applied the reference test and the diagnostic test being evaluated to the entire study population, work-up bias (i.e., when the results of the test being assessed influence whether the reference test is performed) [12] was avoided. Avoidance of review bias (i.e., when persons interpreting the test being investigated have knowledge of the reference test result) was accomplished by 44% of the included studies.

All studies included in this analysis used either histopathologic findings or bone culture results as the reference for the diagnosis of osteomyelitis [24]. The criteria for histopathologic diagnosis were osteonecrosis and infiltration with leukocytes or chronic inflammatory cells, such as lymphocytes or plasma cells. Although these criteria were chosen because they are relatively objective, their limitations must be acknowledged. Bone specimens, obtained either percutaneously or at the time of surgery, may become contaminated, resulting in a false-positive test result, or the infected area may be missed during sampling (i.e., sampling error), resulting in a false-negative test result. Culture results may be false negative if the patient has recently received antibiotic therapy. Histopathologic examination results may be false negative if the bone has evidence of necrosis or inflammation for other reasons.

Neuropathic foot changes, such as Charcot arthropathy, may limit the specificity of imaging findings. Only 3 of the included studies incorporated patients with these foot abnormalities [15, 16, 25]. Data for these patients were not analyzed separately from data for other individuals. Table 3 summarizes the pertinent characteristics of the included studies.

### Diagnosis of Osteomyelitis

#### Clinical examination.

Although soft-tissue infection in a diabetic foot with an ulcer is often clinically obvious, the diagnosis of osteomyelitis underlying a diabetic foot ulcer is challenging. Two clinical findings have been found to have predictive value for osteomyelitis: the size and depth of the ulcer [15] and a positive probe-to-bone test result (i.e., the bone can be probed at the base of the ulcer with use of a sterile steel probe) [28]. Grayson et al. [28] evaluated for osteomyelitis underlying foot ulcers in patients with diabetes with use of the probe-to-bone test. The test had a sensitivity of 0.66 and a specificity of 0.87. The prevalence of osteomyelitis in the study population was high (66%). Shone et al. [29] determined the validity of the probe-to-bone test in a consecutive series of outpatients attending a multidisciplinary clinic. The prevalence of osteomyelitis in this study was 23.5%; the sensitivity was 0.38, and the specificity was 0.91. The disparate results of the 2 studies may be explained, in part, because of differences in study populations. Neither study was included in our review, because not all patients underwent the reference test for diagnosis of osteomyelitis.

Only 1 study evaluating ulcer characteristics predictive of osteomyelitis underlying a foot ulcer in diabetic patients met the inclusion criteria [15]. It was a prospective study with consecutive recruitment, including both outpatients and inpatients. The authors evaluated clinical judgment of the physician who made the diagnosis of osteomyelitis, ulcer area, ulcer inflammation, and bone exposure. Area was determined by multiplying the longest diameter with the widest diameter. Depth
Table 3. Studies of clinical diagnosis and imaging modalities.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Imaging modality (sample size, no. of patients)</th>
<th>Study design</th>
<th>Recruitment</th>
<th>Age, mean years (range)</th>
<th>Prevalence of osteomyelitis</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newman et al. [15] (1991)</td>
<td>Exposed bone (39), radiography (37), bone scan (39), leukocyte scan (39)</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>55 (44–66)</td>
<td>0.68</td>
<td>Blinding not discussed</td>
</tr>
<tr>
<td>Lavery et al. [5] (2007)</td>
<td>Probe-to-bone test (247)</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>51</td>
<td>0.12</td>
<td>…</td>
</tr>
<tr>
<td>Yuh et al. [16] (1989)</td>
<td>Radiography (28a), MRI (29a), bone scan (21a)</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>(32–74)</td>
<td>0.86</td>
<td>Unblinded; inclusion/exclusion criteria not defined; histopathologic criteria for osteomyelitis not defined</td>
</tr>
<tr>
<td>Weinstein et al. [13] (1993)</td>
<td>Radiography (62), MRI (62), bone scan (22)</td>
<td>Prospective</td>
<td>Consecutive</td>
<td>49 (8–23)</td>
<td>0.74</td>
<td>Unblinded; inclusion/exclusion criteria not defined</td>
</tr>
<tr>
<td>Harwood et al. [26] (1999)</td>
<td>Radiography (50), bone scan (47), leukocyte scan (11)</td>
<td>Prospective</td>
<td>…</td>
<td>58</td>
<td>0.70</td>
<td>Blinding not discussed; histopathologic criteria and imaging diagnostic criteria for osteomyelitis not defined</td>
</tr>
<tr>
<td>Newman et al. [17] (1992)</td>
<td>MRI (16), leukocyte scan (16)</td>
<td>Prospective</td>
<td>Not reported</td>
<td>Not reported</td>
<td>0.44</td>
<td>Limited demographic data</td>
</tr>
<tr>
<td>Ertugrul et al. [14] (2006)</td>
<td>MRI (28), leukocyte scan (26)</td>
<td>Prospective</td>
<td>Not reported</td>
<td>62 (40–77)</td>
<td>0.82</td>
<td>Blinding not discussed</td>
</tr>
<tr>
<td>Harvey et al. [27] (1997)</td>
<td>Bone scan (31), leukocyte scan (52)</td>
<td>Retrospective</td>
<td>Not reported</td>
<td>Not reported</td>
<td>0.58</td>
<td>Blinding not discussed; limited methodological data</td>
</tr>
<tr>
<td>Devillers et al. [25] (1998)</td>
<td>Bone scan (25), leukocyte scan (25)</td>
<td>Prospective</td>
<td>Not reported</td>
<td>63 (44–83)</td>
<td>0.60</td>
<td>Unblinded</td>
</tr>
</tbody>
</table>

*a No. of bones.
Table 4. Studies that evaluated clinical examination for diagnosis of osteomyelitis associated with foot ulcer in diabetic patients.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Prevalence of osteomyelitis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive LR</th>
<th>Negative LR</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive LR</th>
<th>Negative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ulcer area ≥2 cm</td>
<td>Ulcer inflammation</td>
<td>Exposed bone and/or probe-to-bone test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newman et al. [15] (1991)</td>
<td>0.68</td>
<td>0.56 (0.36–0.74)</td>
<td>0.92 (0.77–1.06)</td>
<td>7.22</td>
<td>0.48</td>
<td>0.36 (0.18–0.53)</td>
<td>0.76 (0.54–0.99)</td>
<td>1.54</td>
<td>0.83</td>
<td>0.32 (0.14–0.49)</td>
<td>(1.00)</td>
<td>=</td>
<td>0.67</td>
</tr>
<tr>
<td>Lavery et al. [5] (2007)</td>
<td>0.12</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.87 (0.71–0.96)</td>
<td>0.91 (0.89–0.92)</td>
<td>9.40</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**NOTE.** Sensitivity was assessed as the total number of infected patients divided by the number of patients with true positive test results; these proportions were 15/27, 10/28, and 9/28 for ulcer area ≥2 cm, ulcer inflammation, and exposed bone and/or probe-to-bone test, respectively, in Newman et al. [15]. Specificity was assessed as the total number of uninfected persons divided by the number of persons with negative test results; these proportions were 12/13, 10/13, and 13/13, respectively, in Newman et al. [15]. The proportions for sensitivity and specificity for exposed bone and/or probe-to-bone test in Lavery et al. [5] were 26/30 and 197/217, respectively. LR, likelihood ratio; NA, not assessed.
was graded as (1) very deep (exposing bone), (2) moderately deep (≥3 mm, but not exposing bone), or (3) shallow (<3 mm). The prevalence of osteomyelitis was 68%. Exposed bone had 1.00 specificity for diagnosis of osteomyelitis; however, sensitivity was only 0.32. Diagnosis of underlying osteomyelitis on the basis of an ulcer area <2 cm resulted in improved sensitivity (0.56) and a fairly high specificity (0.92); ulcer inflammation had a sensitivity of 0.36 and a specificity of 0.77 (table 4).

A single trial that evaluated the performance of the probe-to-bone test and that used the reference test in all cases was identified [5]. Lavery et al. [5] found that a positive probe-to-bone test result in their unselected outpatient population with diabetes and foot wounds had a sensitivity of 0.87 (95% CI, 0.71–0.96) for diagnosis of osteomyelitis and a specificity of 0.91 (95% CI, 0.89–0.92). The likelihood ratio for a positive test result was 9.40, and the likelihood ratio for a negative test result was 0.14, indicating that a positive probe-to-bone test result is moderately useful in predicting osteomyelitis; more importantly, the probability of osteomyelitis among patients who had negative probe-to-bone test results was very low (0.14).

The pooled diagnostic OR for exposed bone or a positive probe-to-bone test result was 49.45, indicating that a positive test result has excellent discriminatory power to differentiate between the presence or absence of osteomyelitis (table 5). However, it should be acknowledged that this summary OR is based on the results of only 2 studies.

**Diagnostic imaging.** Several imaging tests have been used to assist in the diagnosis of osteomyelitis, including plain radiography, radionuclide bone scan, labeled WBC scan, indium-111 labeled leukocyte scan (usually in conjunction with bone scans), and MRI. CT [30] and positron-emission tomography scans [31] have been inadequately studied for the diagnosis of osteomyelitis in patients with diabetes and foot ulcers; these tests were not included in this review, because neither a histopathologic examination nor culture-based reference was used to diagnose osteomyelitis in those studies.

**Plain radiography.** Four studies of plain radiography met the inclusion criteria [13, 15, 16, 26]. All were prospective studies, and 3 of the 4 used consecutive recruitment [13, 15, 16]. The prevalence of osteomyelitis ranged from 58% to 86%.

Two studies reported that evaluators were not blinded but were provided only limited clinical data [13, 16]. The other 2 studies did not report observer blinding methods [15, 26]. Osteomyelitis was defined as permeative radiolucencies, destructive changes, cortical defects, and/or periosteal new-bone formation by Yuh et al. [16] and Weinstein et al. [13], whereas Newman et al. [15] defined it as cortical erosion in the area of the foot ulcer; Harwood et al. [26] did not report their radiographic criteria.

The sensitivity of plain radiography for diagnosis of osteomyelitis was highly variable, ranging from 0.28 to 0.75. The wide variation may be attributable to the timing of performance of the radiograph in relation to the chronicity of the ulcer. Weinstein et al. [13] and Newman et al. [15] included patients with acute and chronic ulcers. Yuh et al. [16] and Harwood et al. [26] did not report whether ulcers were acute or chronic. The pooled sensitivity was 0.54, and the pooled specificity was 0.68 (table 6). The diagnostic OR was 2.84, with a Q* of 0.60, indicating low-to-moderate accuracy (table 5).

**MRI.** Four trials evaluating the use of MRI met the inclusion criteria [13, 14, 16, 17]. Only 2 of the studies used a consecutive recruitment method [13, 16], but all were prospective trials. MRI reviewers were blinded in the study by Newman et al. [17]. Yuh et al. [16] and Weinstein et al. [13] provided only limited clinical data to evaluators. Ertugul et al. [14] did not discuss methods of blinding. The criteria for diagnosis of osteomyelitis by MRI was low signal intensity on T1-weighted images, high signal intensity on T2-weighted images [13–15], and if performed, short τ inversion recovery sequences in bone marrow.

The prevalence of osteomyelitis ranged from 44% to 86%. The pooled sensitivity was 0.90 (95% CI, 0.82–0.95), and the pooled specificity was 0.79 (95% CI, 0.62–0.91) (table 6). The diagnostic OR was 24.36, indicating excellent discriminant power. The Q* was the highest among all of the diagnostic tests that were studied (table 5).

**Nuclear Medicine Scans**

**Technetium 99 phosphate bone scan.** Six studies of the use of technetium 99 phosphate triple-phase bone scans qualified for inclusion [13, 15, 16, 25–27]. One trial retrospectively eval-

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Studies</th>
<th>Pooled diagnostic OR</th>
<th>Q*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed bone or positive probe-to-bone test result</td>
<td>[5, 15]</td>
<td>49.45</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Radiography</td>
<td>[13, 15, 16, 26]</td>
<td>2.84</td>
<td>0.60</td>
</tr>
<tr>
<td>MRI</td>
<td>[13, 14, 16, 17]</td>
<td>24.36</td>
<td>0.74</td>
</tr>
<tr>
<td>Bone scan</td>
<td>[13, 15, 16, 25–27]</td>
<td>2.10</td>
<td>0.62</td>
</tr>
<tr>
<td>Leukocyte scan</td>
<td>[14, 15, 17, 25–27]</td>
<td>10.07</td>
<td>0.59</td>
</tr>
</tbody>
</table>
uated the accuracy of bone scans for diagnosis of osteomyelitis [27]. Three studies used consecutive recruitment [13, 15, 16]. Two studies reported that evaluators were not blinded but were provided only limited clinical data [13, 16]. Three studies did not discuss observer blinding methods [15, 26, 27]. Devillers et al. [25] did not blind evaluators. Osteomyelitis by imaging study was defined as increased blood flow, blood-pool activity, and abnormally increased intensity localized to the bone. Two trials evaluated results in combination with leukocyte scan results [14, 25]. Two trials did not provide imaging criteria for defining osteomyelitis [26, 27].

The pooled sensitivity and specificity were 0.81 and 0.28, respectively (table 6). The pooled diagnostic OR was 2.10, indicating poor discriminating ability (table 5). The Q* was 0.60, indicating moderate accuracy for diagnosis of osteomyelitis.

**Indium-111–labeled leukocyte scan.** Six studies evaluated the use of indium-111–labeled leukocyte scan for diagnosis of osteomyelitis in diabetic individuals with foot ulcers [14, 15, 17, 25–27]. One study used a retrospective study design [27]. Blinding was not discussed in 4 trials [14, 15, 26, 27], 1 did not blind evaluators [25], and 1 provided limited data to evaluators [17]. The criteria for diagnosis of osteomyelitis was defined as focal abnormal increased activity. Two trials evaluated results in combination with technetium scan results [14, 25]. Two trials did not provide imaging criteria for defining osteomyelitis [26, 27].

The pooled sensitivity of indium-111–labeled leukocyte scan was 0.74 (95% CI, 0.67–0.80), and the pooled specificity was 0.68 (95% CI, 0.57–0.78) (table 6). Heterogeneity was present in both the estimates of sensitivity and specificity. The pooled diagnostic OR was 10.07, revealing moderately good discriminating characteristics. The Q* of 0.59 indicated low-to-moderate accuracy for diagnosis of osteomyelitis (table 5).

**DISCUSSION**

The diagnosis of osteomyelitis underlying a diabetic foot ulcer is challenging. Few clinical features are useful in making the diagnosis. In general, the results of laboratory tests, such as sedimentation rate, are nonspecific, although a recent retrospective pilot study that compared patients with osteomyelitis with those with cellulitis found that an erythrocyte sedimentation rate of 70 mm/h had a sensitivity of 0.89 and specificity of 1.00 for diagnosis of osteomyelitis [32]. Several imaging tests for diagnosis of osteomyelitis in a diabetic foot ulcer are available; however, many studies that assess the diagnostic performance characteristics of these tests have limitations regarding choice of reference test to conclusively establish the diagnosis of osteomyelitis. In our review, in which we included only studies that used histopathologic examination or microbiologic culture of bone specimens, we found that among the clinical examination techniques that are useful for diagnosis of osteomyelitis, the criterion most suggestive of osteomyelitis is the presence of exposed bone or a positive probe-to-bone test result. However, the probe-to-bone test has low sensitivity.

Among the imaging tests that we evaluated, MRI was the most accurate. However, MRI is costly and may not be readily available. Nuclear medicine bone scan and indium-labeled leukocyte scans had low-to-moderate accuracy for detection of osteomyelitis. Plain radiographs provided limited information; however, studies did not correlate the results of plain radiographs with the duration of ulcer. This is important because early osteomyelitis may not be accurately identified by plain radiographs. Often, in clinical practice, if there is evidence of soft-tissue infection associated with an open wound and plain radiograph findings are negative, empirical therapy for soft-tissue infection is given. Radiographs may then be performed again in 2–3 weeks; if the findings are positive, further assessment and treatment of osteomyelitis should be undertaken with use of bone sampling [33].

The diagnosis of osteomyelitis has been reviewed in previous studies [6, 24, 34]; however, a systematic assessment and quantitative synthesis of the data and incorporation of the clinical examination findings have been lacking. A previous review that assessed the accuracy of imaging tests for osteomyelitis also found that MRI was markedly superior to other imaging tests. This is congruent with the results of our analysis. However, studies of clinical examination features were not included in that review, and the authors included patients with and without diabetes and with and without open wounds [35].

An important factor to take into account during the assess-

**Table 6. Summary statistics of imaging modalities for diagnosis of osteomyelitis associated with diabetic foot ulcer.**

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Studies</th>
<th>Pooled sample</th>
<th>Pooled sensitivity (95% CI)</th>
<th>Pooled specificity (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe-to-bone test or exposed bone</td>
<td>[5, 15]</td>
<td>288</td>
<td>0.60 (0.46–0.73)</td>
<td>0.91 (0.86–0.94)</td>
<td>.11</td>
</tr>
<tr>
<td>Radiography</td>
<td>[13, 15, 16, 26]</td>
<td>177</td>
<td>0.54 (0.44–0.63)</td>
<td>0.68 (0.53–0.80)</td>
<td>.01</td>
</tr>
<tr>
<td>MRI</td>
<td>[13, 14, 16, 17]</td>
<td>135</td>
<td>0.90 (0.82–0.95)</td>
<td>0.79 (0.62–0.91)</td>
<td>.41</td>
</tr>
<tr>
<td>Bone scan</td>
<td>[13, 15, 16, 25–27]</td>
<td>185</td>
<td>0.81 (0.73–0.87)</td>
<td>0.28 (0.17–0.42)</td>
<td>.01</td>
</tr>
<tr>
<td>Leukocyte scan</td>
<td>[14, 15, 17, 25–27]</td>
<td>269</td>
<td>0.74 (0.67–0.80)</td>
<td>0.68 (0.57–0.78)</td>
<td>.61</td>
</tr>
</tbody>
</table>

* For heterogeneity for sensitivity.
ment of the performance of diagnostic tests is the pretest probability (i.e., prevalence) of disease [36]. In a population with a low prevalence of infection, even a test with high sensitivity and specificity will have low predictive values. Wrobel et al. [36] revealed that, with a pretest probability of 0.25, the positive predictive value of MRI was 0.66, compared with a positive predictive value of 0.85 for a pretest probability of 0.50. In our review, the prevalence of osteomyelitis ranged from 0.12 to 0.86; thus, the populations studied varied considerably. It is unclear why such a high prevalence of osteomyelitis was noted in the study by Newman et al. [15], particularly because the study population represented an unselected population. Because the pretest probability is usually not known precisely at the time when diagnostic testing is pursued, it may be advisable to calculate the expected posttest probabilities on the basis of a range of pretest probabilities, to determine whether the test results will meaningfully affect subsequent decision making. One such tool is the Fagan’s nomogram [37], which allows estimation of the posttest odds using the likelihood ratio (in this case, the diagnostic OR).

Our review has several limitations. There was only a very limited number of studies that evaluated clinical examination techniques for diagnosis of osteomyelitis; thus, robust estimates were not possible. We found heterogeneity in our pooled estimates of sensitivity and specificity. Many of the studies had methodologic limitations that affected rigorous assessment of the diagnostic test studied. We applied strict inclusion criteria that required studies to provide sensitivity and specificity information; this may have excluded some pertinent studies. The findings of the clinical examination and imaging studies would be expected to depend on the chronicity of the ulcer, and this was not reported in many of the included studies.

In conclusion, clinical features that suggest osteomyelitis include the presence of exposed bone and a positive probe-to-bone test result. However, the number of studies that have assessed clinical features to aid in diagnosis of osteomyelitis are limited. Among the various imaging modalities available, MRI is the most accurate. As with most other diagnostic tests, the predictive value is heavily influenced by the underlying prevalence of disease.

Acknowledgments

Financial support. National Institutes of Health to the University of Wisconsin School of Medicine and Public Health (5 K12 AG019247–05 to R.S.).

Potential conflicts of interest. All authors: no conflicts.

References

26. Harwood SJ, Valdivia S, Hung GL, Quenzer RW. Use of Sulesomab, a


