# Does This Patient With Diabetes Have Osteomyelitis of the Lower Extremity?

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## RATIONAL CLINICAL EXAMINATION REVIEW SOURCE

This is a rational clinical examination abstract, a regular feature of the *Annals*' Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a rational clinical examination review from the *Journal of the American Medical Association* and a commentary by an emergency physician knowledgeable in the subject area.

The source for this rational clinical examination review abstract is: Butalia S, Palda VA, Sargeant RJ, et al. Does this patient with diabetes have osteomyelitis of the lower extremity? *JAMA.* 2008;299:806-813. The *Annals*' EBEM editors assisted in the preparation of the abstract of this rational clinical examination review, as well as selection of the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

To summarize the test characteristics of the medical history, physical examination, routinely available laboratory measurements, radiographs, and magnetic resonance imaging (MRI) for evaluating lower extremity osteomyelitis in patients with diabetes.

## DATA SOURCES

The authors conducted an English-language search of MEDLINE (1966 to March 2007) for articles related to osteomyelitis in diabetic patients. A hand search of references from retrieved articles, previous reviews, and polling experts was also performed.

## STUDY SELECTION

One author screened potential articles from the MEDLINE search. Two other investigators independently reviewed these studies in detail for inclusion criteria and graded the quality of the study with a standardized instrument. Three criteria were necessary for an article to be included in this review: original research of medical history, physical examination, laboratory testing, or radiographic imaging in the diagnosis of lower extremity osteomyelitis in diabetic patients; reporting of operating characteristics of the diagnostic test; and comparison of the diagnostic test with a reference standard. Studies of pediatric or nondiabetic populations were excluded. The authors also included data from one high-quality meta-analysis of MRI in diabetic lower extremity infections that was not captured in their original search strategy.

## DATA ANALYSIS

Bone biopsy was the reference standard for the diagnosis of osteomyelitis, with a positive result defined by either culture or histologic confirmation because many subjects had previously received antibiotics. Each study had a likelihood ratio predicting the presence of osteomyelitis calculated for each outcome of interest with published raw data. If 2 or more studies examined the same variable, a 95% confidence interval (CI) was calculated.

## MAIN RESULTS

Although the authors fully reviewed 21 studies including 1,027 patients, none addressed the utility of historical criteria for the diagnosis of osteomyelitis of the lower extremity in patients with diabetes. Furthermore, only 1 Level II study was identified, in addition to 9 Level III studies. No study was ED based. Instead, patient populations were a variety of inpatient and outpatient cohorts with foot ulcers and suspected osteomyelitis. One retrospective review of almost 9,000 patients suggested that 15% of subjects with a foot ulcer developed osteomyelitis at or after diagnosis. Although no study assessed the precision of physical examination findings, the presence of ulcer greater than 2 cm and the "probe-to-bone" test were both clinically useful for increasing or decreasing the likelihood of osteomyelitis. A positive probe-to-bone result is defined by the presence of hard, gritty material at the

wound base, noted with a sterile blunt steel probe, without soft tissue noted between bone and probe.

For ancillary testing, an elevated erythrocyte sedimentation rate and abnormal radiograph results (focal loss of trabecular bone, periosteal reaction, or frank bone destruction) were both helpful. The rational clinical examination authors combined studies assessing clinical judgment with those using a previously described ulcer assessment tool called the Wagner Grading Scale (a scale that also depends on subjective assessment variables). Overall, a positive "clinical gestalt" was almost as useful as ulcer size or probe-to-bone test. No diagnostic test other than MRI was useful for ruling out osteomyelitis. The single MRI meta-analysis included 11 studies totaling 275 patients, with a summary negative likelihood ratio of 0.14 (95% CI 0.08 to 0.26). This meta-analysis demonstrated that MRI was superior to bone scans, WBC count scans, and plain radiography for the diagnosis of osteomyelitis.

## CONCLUSIONS

An ulcer area larger than 2 $cm^2$, a positive probe-to-bone test result, an ESR greater than 70 mm/hour, and an abnormal radiograph result are helpful in diagnosing the presence of lower extremity osteomyelitis in patients with diabetes. A negative MRI result makes the diagnosis much less likely when all of these findings are absent. No single historical feature or physical examination result reliably excludes osteomyelitis. The diagnostic utility of a combination of findings is unknown.

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**Table.** Diagnostic criteria for osteomyelitis of the lower extremity in patients with diabetes.

| Diagnostic Criteria | Positive LR (95% CI) | Negative LR (95% CI) |
|---|---|---|
| Ulcer size <2 $cm^2$ | 7.2 (1.1–49) | 0.48 (0.31–0.76) |
| Positive probe-to-bone test result | 6.4 (3.6–11)* | 0.39 (0.20–0.76) |
| Clinical gestalt | 5.5 (1.8–17)* | 0.54 (0.30–0.97) |
| ESR >70 mm/h | 11 (1.6–79)* | 0.34 (0.06–1.90) |
| Abnormal radiograph result | 2.3 (1.6–3.3)* | 0.63 (0.51–0.78) |
| Positive MRI result | 3.8 (2.5–5.8)* | 0.14 (0.08–0.26) |

*LR,* Likelihood ratio; *ESR,* erythrocyte sedimentation rate.
*Summary likelihood ratio.

## COMMENTARY: CLINICAL IMPLICATION

Although diabetic foot complications are common in today's emergency department (ED), there is a paucity of emergency medicine–specific research on disease epidemiology, diagnostic, therapeutic, or prognostic approach.[1,2] Currently, almost 200 million individuals worldwide have diabetes, and by 2025 the prevalence will increase to 333 million because of longer life expectancy, sedentary lifestyle, and changing dietary habits.[3] In the United States, more than 30% of diabetics have lower extremity disease, including 7.7% with ulcers.[4] One of the most dreaded diabetic foot complications is osteomyelitis-related limb amputation, which is more than 10-fold more common in diabetic patients than in nondiabetic patients.[5,6] Although 85% of diabetic amputations are preceded by minor trauma, leading to cutaneous ulceration and failed wound healing,[7] identifying patients at increased risk for amputation is not easily accomplished in the ED.[8] In addition, in one sample more than half of ED patients were found to be at risk for undiagnosed diabetes.[9] In another study, 67% of screened ED patients had diabetes or prediabetes.[10] Therefore, one of the first steps in diagnosing a diabetic foot ulcer that may be osteomyelitis may be recognizing the presence of diabetes mellitus.

Once the diagnosis of diabetes has been recognized, understanding the limited diagnostic test characteristics of medical history and physical examination for recognizing lower extremity osteomyelitis is essential (Table). An ulcer size exceeding 2 $cm^2$ or a positive probe-to-bone test is the only physical examination element that substantially increases the likelihood of diabetic osteomyelitis above the 15% pretest probability suggested by the current review. The current review, however, does not isolate ED patients. In addition, only those patients with culture or bone biopsy are included, indicating that the population under study was likely to have been a group for whom treating physicians had an unusually high clinical suspicion of disease.

Although clinical gestalt seemed to establish the diagnosis of diabetic osteomyelitis, as well as ulcer size and bone-to-probe test, the original articles failed to describe the elements encompassing clinical intuition. In addition, the authors focus on the Wagner grade, which they conflate with clinician judgment. The Wagner system involves a bedside assessment of ulcer depth, osteomyelitis findings, and gangrene. Another risk-stratification system has been developed that may better predict amputation risk (by assessing ulcer depth, infection presence, and lower extremity ischemia signs)[11]; however, it was not included in this review.

An ESR elevated more than 70 mm/hour is a useful laboratory test to increase the likelihood of diabetic osteomyelitis, although the summary likelihood ratio is based on 4 low-quality studies totaling 108 subjects. Other commonly ordered laboratory tests such as WBC count and swab culture are not useful to rule in or rule out this diagnosis. Although abnormal radiograph results are useful to increase the likelihood of diabetic osteomyelitis, a normal radiograph result does not significantly decrease the likelihood. In fact, the only test that does significantly decrease the posttest probability of diabetic osteomyelitis is MRI. Unfortunately, access to MRIs may be an issue for many populations, limiting the utility of this imaging modality.[12] The authors did not assess nuclear imaging for the diagnosis of osteomyelitis.

## TAKE-HOME MESSAGE

Ulcer size greater than 2 cm and a positive bone-to-probe test result each increases the likelihood of diabetic osteomyelitis. An ESR greater than 70 mm/hour strongly suggests the diagnosis in the correct clinical setting. Although abnormal radiograph results can increase the probability, only MRI substantially reduces the likelihood of lower extremity osteomyelitis in a diabetic patient.

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## EBEM TEACHING POINT

**Verification bias.** The diagnostic performance of a test is determined by comparing it with an established criterion standard test (formerly called "gold standard" and now commonly "reference standard") that is the most accurate established test for the disease. In this rational clinical examination, bone biopsy was considered the reference standard for osteomyelitis and tests such as ulcer size were evaluated. If the presence of osteomyelitis is determined by performance of bone biopsy on every patient, then an unbiased assessment of ulcer size as a test for osteomyelitis results. Unfortunately, the expense and invasiveness of bone biopsy may prompt investigators to obtain it selectively. This has been labeled "verification bias" or "workup bias" because often only those patients believed to have a high likelihood of disease are fully evaluated, ie, undergo bone biopsy. This may mean that those patients with a positive result on the test being evaluated (ulcer size) are more likely to have the full evaluation, including bone biopsy, which leads to false "verification" of ulcer size by ensuring that those with larger ulcers are more likely to undergo bone biopsy, whereas those with smaller ulcers will either not be included in the data or will be presumed, perhaps falsely, to be disease negative. The main result of this bias will be erroneous elevation of sensitivity and specificity.

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