REVIEW ARTICLE

Diagnosing Diabetic Foot Osteomyelitis: Narrative Review and a Suggested 2-Step Score-Based Diagnostic Pathway for Clinicians

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The diabetic foot infection remains a major cause of morbidity and mortality in many patients and remains a challenging diagnosis for most clinicians. Diagnosis is largely based on clinical signs supplemented by various imaging tests. Magnetic resonance imaging (MRI) is not readily available to many clinicians, and bone biopsy, which is the accepted criterion standard for diagnosis, is rarely performed routinely. This evidence-based review and the proposed diagnostic scoring pathway substratifies the current International Working Group on the Diabetes Foot guidelines for diagnosing diabetic foot osteomyelitis into a convenient 2-step diagnostic pathway for clinicians. This proposed diagnostic approach will need further validation prospectively, but it can serve as a useful diagnostic tool during the initial assessment and management of diabetic foot infections. A MEDLINE search of English-language articles on diabetic foot osteomyelitis published between 1986 and March 2014 was conducted. Additional articles were also identified through a search of references from the retrieved articles, published guidelines, systematic reviews, and meta-analyses.

Keywords. diabetes; diabetic foot; diagnosis; infection; osteomyelitis; systematic review.

The importance of early diagnosis of diabetic foot osteomyelitis cannot be understated. Diabetic foot infection is now the most frequent cause for hospital admissions and carries with it a significant risk of increased morbidity and mortality [1]. One to 4 percent of diabetics develop foot ulcers annually, and 85 percent of lower extremity amputations in diabetics are preceded by a foot ulcer. Five-year mortality rates of 45 percent for neuropathic ulcers and 47 percent for postfoot amputations have been reported [2, 3]. Early diagnosis remains a challenge for many reasons. Magnetic resonance imaging (MRI) is not readily available to many clinicians, and a bone biopsy, which is the accepted criterion standard for diagnosis, is rarely performed routinely. Moreover, there seems to be an overuse of certain investigations such as the bone scan in the initial diagnosis of osteomyelitis. Initial assessment by a clinician involves the complex process of estimating the likelihood of underlying osteomyelitis based on the available clinical data and then deciding on the appropriate laboratory and radiological investigations. This process involves time and resources, and, unless there is an objective direction to this decision-making process from the outset, there remains a chance of either a missed diagnosis or an over diagnosis of osteomyelitis. A missed diagnosis has a high likelihood of collective morbidity and mortality for the patient, along with the increased risk of with undesirable limb amputation, and over-diagnosis results in soaring healthcare costs, overutilization of healthcare resources, and injudicious use of antimicrobials.

Magnetic resonance imaging is considered the most accurate radiological test, and bone biopsy is the gold standard when 1 or more pathogens are cultured from

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the bone along with histo-pathological changes consistent with acute or chronic inflammation [4]. Magnetic resonance imaging scanning is not widely available, and other issues with MRI include high costs and availability of musculoskeletal radiologists skilled in interpreting the MRI scans. Bone biopsy is rarely performed on a routine basis. The obstacles include a lack of routine setup to perform foot bone biopsies, clinicians lacking training in performing the procedure, and the perceived risk of adverse events. There are 2 other important factors that affect the early diagnosis of diabetic foot osteomyelitis: (1) it may take several weeks for the osteomyelitis to produce defects on plain radiographs; and (2) the presence of diabetic neuro-osteoarthropathy, which may closely resemble diabetic foot osteomyelitis or may even coexist with it [5].

The Infectious Diseases Society of America (IDSA) and the International Working Group on Diabetic Foot (IWGDF) have proposed guidelines for the diagnosis of diabetic foot osteomyelitis [4, 6]. The Infectious Diseases Society of America guidelines suggest obtaining initial and serial plain radiographs and considering additional imaging studies, preferably MRI scanning, if the clinical suspicion for osteomyelitis remains high [6]. The IWGDF has proposed consensus criteria for diagnosing osteomyelitis based on the overall probability of osteomyelitis from the findings on MRI scanning, bone sampling, and clinical parameters [4]. The "definite" category, with an estimated posttest probability of more than 90%, includes positive bone cultures and positive histology, or bone purulence, or atraumatically detached bone fragments removed from ulcer by surgeon, or an intraosseous abscess on MRI scan. The "probable" category, with an estimated 51%–90% posttest probability, includes visible cancellous bone in ulcer, or MRI with signs of bone edema along with other signs of osteomyelitis, or a bone sample with either positive culture or a positive histology. "Possible" category, with 10%–50% posttest probability, includes cortical destruction on plain radiograph, or an erythrocyte sedimentation rate (ESR) of more than 70 without any other plausible explanation, or a positive probe-to-bone ([PTB] or visible cortical bone), or a nonhealing wound for more than 6 weeks despite perfusion or 2 weeks with evidence of infection. Any 2 probable criteria or 1 probable and 2 possible criteria or any 4 possible criteria are considered to have a combined posttest probability of more than 90%.

SUMMARY OF THE AVAILABLE EVIDENCE IN THE DIAGNOSIS OF THE DIABETIC FOOT OSTEOMYELITIS

History and "Clinical Gestalt"

No reviewed studies identified the utility of any component of history in the diagnosis of diabetes foot osteomyelitis. Butalia et al [7] noted that the clinical impression of osteomyelitis without formal objective criteria increased the likelihood of osteomyelitis with a summary positive likelihood ratio (+LR) of 5.5 and a negative likelihood ratio of 0.54. This finding seems to suggest that subjective "clinical judgment" is more helpful in detecting the presence of osteomyelitis rather than detecting its absence. Two selected studies in this review used the Wagner grading scale to describe the diagnostic accuracy of clinical judgment [7–9].

Ulcer Size and Ulcer Inflammation

A prospective cohort study evaluating the presence or absence of inflammation and bone exposure reported that an ulcer area larger than 2 cm^2 makes osteomyelitis more likely with a +LR of 7.2 and a sensitivity and specificity of 0.56 and 0.92, respectively [6–8]. The presence or absence of signs of inflammation does not affect the probability of underlying osteomyelitis with a reported +LR of 1.5 and a negative likelihood ratio of 0.84 [7, 8, 10, 11].

Inflammatory Markers and Blood Tests

An elevated ESR level of more than 70 mm/hour increases the likelihood of osteomyelitis in a diabetic foot with a pooled +LR of 11 (confidence interval [CI], 1.6–79) and a negative likelihood ratio of 0.34 [7]. In another recent study, ESR remained high for 3 months only in patients with bone infection and was recommended to be used for the follow up of patients with osteomyelitis [13]. Erythrocyte sedimentation rate currently remains the most useful and most studied laboratory test in the diagnosis of diabetic foot osteomyelitis [14, 15]. One study reported on the usefulness of C-reactive protein (CRP) value greater than 3.2 mg/dL in distinguishing osteomyelitis from soft tissue infection, with the univariate odds ratio of 10.8 and P value < .001 [16]. However, in another study, both neutrophil count and CRP were higher in patients with soft tissue infection without osteomyelitis compared with those with osteomyelitis [17]. There is limited published data on the usefulness of CRP (compared with ESR) or procalcitonin in the diagnosis of diabetic foot osteomyelitis [18]. In its diagnostic guidelines, the IWGDF lists elevated ESR to more than 70 mm/hour (in the absence of any other plausible explanation) as one of the possible criteria in the proposed scheme for diagnosis of diabetic foot osteomyelitis. Swab cultures and elevated white blood cell (WBC) counts have no clear diagnostic utility in the diagnosis of diabetic foot osteomyelitis [8, 12].

Bone Exposure and Probe-to-Bone Tests

The presence of exposed bone has a +LR of 9.2 [8]. Striking bone with a blunt, sterile metal probe increases the likelihood of osteomyelitis in accordance with the pretest probability of osteomyelitis. In various studies, the +LR for a positive PTB test ranged from 4.3 to 9.4 if the pretest probability of bone infection was high (eg, >50%) [7, 10, 19–22]. Therefore, a positive PTB in an infected wound is highly suggestive of osteomyelitis, whereas a negative PTB test does not exclude the diagnosis. In uninfected ulcers or in a patient at a low risk, osteomyelitis is

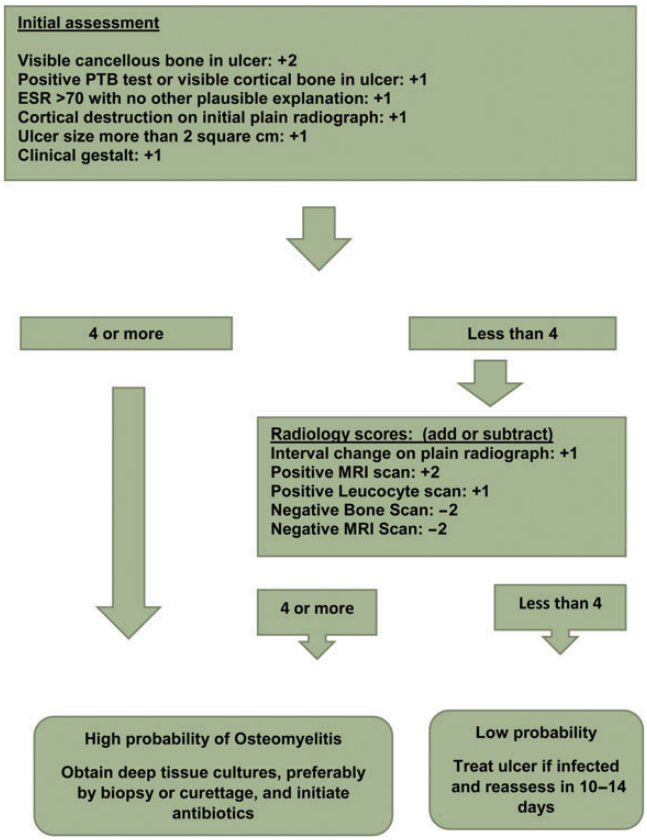

Fig. 1. Diagnostic pathway for diabetic foot osteomyelitis.

unlikely if the test is negative; and the PTB test has a low specificity if positive.

Plain Radiographs in the Diagnosis of Diabetic Foot Osteomyelitis

Dinh et al [10] reported a pooled sensitivity and a pooled specificity of 0.54, and 0.68 and a diagnostic odds ratio of 2.84, with a Q statistic of 0.60 for plain radiography in the diagnosis of osteomyelitis. This result indicates low to moderate accuracy as a diagnostic method, which is likely due to the fact that it can take up to 3 to 4 weeks for changes to show up on a plain radiograph and none of the selected studies evaluated serial plain radiographs. Another review, which included 7 studies, reported a +LR of 2.3 and a negative likelihood ratio of 0.63 [7, 23, 24]. It seems that changes in the plain radiography over a period of time may be more useful than a single study.

Technetium-99 Triple-Phase Bone Scanning

In a systematic review, Capriotti et al [25] reported a sensitivity of 0.90 and a specificity of 0.46 for triple-phase bone scans in

Table 1. Interpretation of Diagnostic Findings

Diagnostic Test	Positive LR	Negative LR	Approximate Increase in Probability if Positive (%)	Approximate Decrease in Probability if Negative (%)
Exposed Bone	9.2 (0.57–146)	0.70 (0.53–0.92)	+ (40–45)	Less than 15
Ulcer area >2 square cm	7.2 (1.1–49)	0.48 (0.31–0.76)	+ (35–40)	– (15 to 20)
ESR >70 with no other plausible explanation	11 (1.6–79)	0.34 (0.06–1.9)	+ (45–50)	– (20 to 25)
Probe-to-bone testing	6.4 (3.6–11)	0.39 (0.20–0.76)	+ (35–40)	– (20 to 25)
Plain radiograph at presentation	2.3 (1.6–3.3)	0.63 (0.5–8.8)	+ (15–20)	Less than 15
Clinical gestalt*	5.5 (0.51–4.7)	0.54 (0.30–0.97)	+ (30–35)	Less than 15

Abbreviations: ESR, erythrocyte sedimentation rate; LR, likelihood ratio.

* Including nonhealing wound for >6 weeks despite perfusion or ulcer >2 weeks duration with evidence of infection.

Table 2. Proposed Scoring System for the Initial Diagnosis of Diabetic Foot Osteomyelitis*

Criteria	Score
Visible cancellous bone in ulcer	2
Positive PTB test or visible cortical bone in ulcer	1
ESR >70 with no other plausible explanation	1
Cortical destruction on initial plain radiograph	1
Ulcer size more than 2 square cm	1
Clinical gestalt: nonhealing wound for >6 weeks despite perfusion or ulcer >2 weeks duration with evidence of infection	1
Radiology Scores: (add if initial score less than 4)	
Positive leukocyte scan: +1	
Interval change (minimum 2 weeks) on plain radiograph: +1	
Positive MRI scan: +2	
Negative MRI scan: −2	
Negative bone scan: −2	

Abbreviations: ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; PTB, probe to bone.

* Score: 4 or more, high posttest probability of osteomyelitis. Less than 4: add radiology scores.

the diagnosis of osteomyelitis [26]. Another review reported a pooled sensitivity of 80% but a specificity of only 28%, with pooled diagnostic odds ratio of 2.1 and a Q statistic of 0.6 [10]. Therefore, if the bone scan is negative, it likely rules out osteomyelitis, but the number of false positives are too high given the low specificity. Focal hyperperfusion, hyperemia, and bony uptake can also be seen in other pathological conditions such as fractures, neuropathic joints, and chronic soft tissue infections. Almost any inflammatory condition will cause increased uptake, and a bone scan may remain positive for up to 4 months after successful therapy. The best value of the bone scan is as a screening test if the index of suspicion for osteomyelitis is low [25]. A negative result makes osteomyelitis unlikely, whereas a positive test does not confirm it [25].

Radiolabeled White Blood Cell Scanning

Indium-111-labeled or Technetium-99-labeled leucocytes are not taken up by healthy bone and do not usually accumulate at the site of new bone formation without infection. Therefore, specificity of leucocyte scans is better than triple-phase bone scan, but spatial resolution can be a limiting factor. Technetium-99 labeling seems to provide superior spatial resolution compared with Indium 111-labeled scans. Dinh et al [10] reported pooled sensitivity of 0.74 and a specificity of 0.68 for leukocytes scans. The pooled diagnostic odds ratio in this review was 10, with Q statistic of 0.59. Another review reported positive predictive values of 70%–90% and negative predictive values of 81%–83% for Technetium- and Indium-labeled scans, respectively [25]. White blood cell scans are more useful than bone scans in the diagnosis and evaluation of the extent of osteomyelitis, as well as during the follow up of medical treatment [25]. The United Kingdom National Institute for Health and Care Excellence guidelines suggest WBC scanning as the next test when osteomyelitis is suspected and MRI is unavailable or contraindicated. Sensitivity can be a low in an ischemic foot or a foot with poor blood supply. There is no clear diagnostic benefit of combined bone scan and WBC scan. It is expensive, time consuming, and still less specific than MRI [27].

Magnetic Resonance Imaging

Among the radiological investigations, MRI has the best diagnostic value. It reveals active medullary osteomyelitis as an area of abnormal marrow with decreased signal intensity on T1-weighted images that correspond to an area of high intensity on T2-weighted images. In addition, it is also quite useful for assessing the extent and the anatomy of deep soft tissue infections. Specificity can be affected by difficulty in distinguishing osteomyelitis from other causes of marrow edema, including acute diabetic neuro-osteoarthropathy. Various studies have reported a pooled sensitivity of approximately 0.90 (CI, 0.82–0.95), specificity of approximately 0.85, with a diagnostic odds ratio of 24.4, indicating excellent discriminant power [7, 10, 24].

Other Diagnostic Modalities

There have been some studies evaluating computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) scans for the diagnosis of osteomyelitis. Fluorodeoxyglucose-PET scan has been reported to have high sensitivity ranging from 0.94 to 1.00 and specificity ranging from 0.87 to 1.00 [26]. One study reported even better diagnostic accuracy with the combination of FDG-PET and CT scan [28].

PROPOSED SCORE-BASED MODEL FOR THE INITIAL DIAGNOSIS OF DIABETIC FOOT OSTEOMYELITIS (FIGURE1)

Score of 4 or More on Initial Evaluation

High Probability of Osteomyelitis

Obtain cultures either by biopsy or curettage, and after the wound has been cleansed and debrided. The specimen must be placed in a sterile system and delivered to the laboratory for aerobic and anaerobic cultures. Avoid swab specimens or specimens from inadequately debrided wounds. Bone biopsy is the preferred method of sample collection for culture when osteomyelitis is suspected. Percutaneous sampling through uninvolved tissue under radiographic guidance is a useful technique [6].

Score of Less Than 4 on Initial Evaluation

Obtain radiology tests and add radiology scores. If added scores are more than 4, then there is high probability of osteomyelitis as described above.

Combined Score of Less Than 4

Low Probability of Osteomyelitis

Treat ulcer if infected and reassess in 10–14 days.

Rationale for the Scoring Criteria and Conformity With the Existing Guidelines

The posttest probability of a test depends upon the likelihood ratio. The bigger the number in a +LR, the more convincingly the finding suggests the disease. The reverse is true for a negative likelihood ratio. In a manner that simplifies the interpretation of likelihood ratios in clinical use, these estimates are accurate to within 10% of the calculated values for all pretest probabilities between 10% and 90%, with an average error of approximately 4% [29] (Table 1).

This diagnostic scoring takes into account the clinical and radiological criteria for diagnosis of osteomyelitis as proposed by the IWGDF guidelines [4]. In Table 2, diagnostic tests with posttest probability of between 10% and 50% identified as possible criteria in the IWGDF guidelines have been assigned a score of 1. "Visible cancellous bone in an ulcer" is assigned a probable category in the IWGDF guidelines and therefore assigned a score of 2 in this pathway. Good quality evidence suggests that ulcer area of more than 2 square centimeters makes osteomyelitis more likely [6–8]. It is therefore assigned a score of 1. A nonhealing wound for more than 6 weeks despite perfusion or an ulcer of more than 2 weeks duration with evidence of infection suggests increased likelihood of osteomyelitis and has been listed as one of the possible criteria in the IWGDF diagnostic scheme. It is therefore assigned a score of 1. A negative bone scan and a negative MRI have a high negative predictive value and have been assigned a score of −2. The IDSA guidelines and a recent study emphasize the diagnostic value of abnormalities seen on an initial or serial plain radiographs and PTB testing.

The IWGDF classification defines a "definite" probability of diabetic foot osteomyelitis based on 1 probable plus at least 2 possible criteria, or at least 4 possible criteria. This criteria is automatically validated in this proposed scoring pathway as an initial score of more than 4 and hence a high likelihood of foot osteomyelitis. The important difference with this scoring pathway is that the initial score is based entirely on the information that is readily available to the examining clinician. This approach helps in stratifying the risk of osteomyelitis at the initial assessment and provides direction for further diagnostic imaging. The final score after obtaining additional radiological investigations further quantifies the likelihood of osteomyelitis and directs the management strategy.

The limitation of this diagnostic proposal, as well as the published IWGDF diagnostic guidelines, is that it needs to be validated prospectively. Therefore, at this stage, it can only serve as a diagnostic tool for estimating the likelihood of osteomyelitis rather than a means for confirming or rejecting the diagnosis. However, the approach suggested in this model may prevent overreliance on certain investigations (such as "bone" scans) as the initial investigation of choice for all suspected osteomyelitis, and provide a basis for judicious use of healthcare resources and antimicrobials in the management of diabetic foot infections.

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