Continuing Medical Education

Radiographic Evaluation of Infection: An Update

Sometimes less advanced is better.

BY JARROD SHAPIRO, DPM

Objectives

1) Understand the role of advanced imaging for the diagnosis of osteomyelitis.

2) Understand where radiographs and clinical decision-making fit into the diagnosis of osteomyelitis.

3) Apply the concept of pre-test probability to decision-making.

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A 65 year-old diabetic male is admitted to the hospital for cellulitis of the right foot. He has a 2-cm deep ulcer on the plantar aspect of the foot that has been present for four months. This ulcer has been recurrent with repeated closures and re-ulceration. The wound probes to the periosteum of the fifth metatarsal head and the dorsalis pedis, and posterior tibial pulses are non-palpable (Figure 1).

Radiographs (Figure 2) reveal questionable periostitis of the fifth metatarsal head but no frank erosion. At this point, the clinician must determine the next step in evaluation, including ordering serum blood work and whether or not to order an advanced imaging study. In many hospitals in the United States magnetic resonance imaging (MRI) is the imaging study of choice to diagnose pedal osteomyelitis.

Radiographs are not the most sensitive imaging method to diagnose osteomyelitis because changes lag behind the clinical course.

However, a more nuanced consideration of the use of advanced imag-

ing is necessary for the modern lower extremity specialist to most appropriately utilize this and other diagnostic methods. The following discussion will make three primary assertions.

1) Advanced imaging is rarely needed to diagnose pedal osteotomyelitis.

2) When MRI is used for the diagnosis of osteomyelitis of the foot, a detailed imaging interpretation is mandatory.

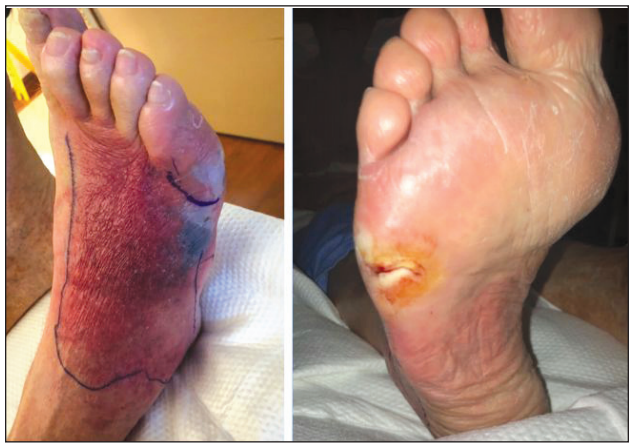


Figure 1: Clinical presentation demonstrating dorsal erythema, early necrosis, and a plantar ulceration.

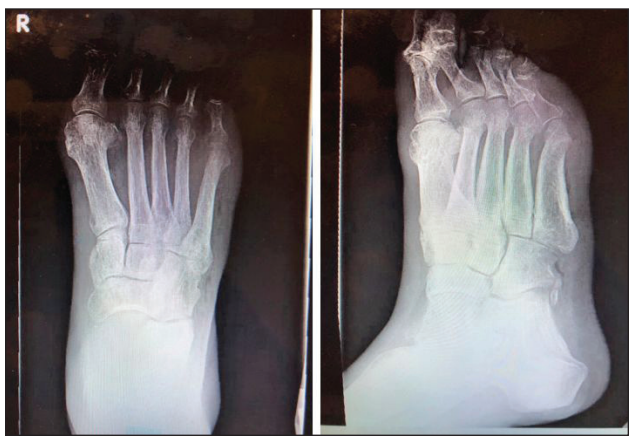


Figure 2: Dorsoplantar and medial oblique radiographs demonstrating questionable periostitis with subtle erosion of the fifth metatarsal head.

Magnetic resonance imaging is the most sensitive and specific.

3) A logical clinical approach to the diagnosis of pedal osteomyelitis is best.

What Does the Literature Say About Imaging Methods to Diagnose Osteomyelitis?

The most common imaging method obtained by podiatric physicians is the foot radiograph. The benefits of this imaging modality are its availability and ease to obtain. However, radiographic changes consistent with osteomyelitis are known to lag behind the clinical course of the infection, affecting its sensitivity. Additionally, the predictive power is lower than with other modalities, with a published pooled sensitivity of 0.68.[7] Specificity is much higher at 80%,[24] which makes it more useful when changes are seen. Avaro-Afonso and colleagues found cortical disruption to be the most accurate radiographic characteristic for the diagnosis of pedal osteomyelitis with 0.76 sensitivity but lower 0.47 specificity.[2]

The Infectious Disease Society of America currently recommends obtaining radiographs on all patients presenting with a diabetic foot infection, looking for bone changes, gas, and radio-opaque foreign bodies.[19] Importantly, obtaining serial radiographs (multiple repeated images over time) may be highly effective in uncertain cases and for monitoring the effectiveness of treatment. Other imaging methods, such as nuclear isotopic scans (e.g, Technesium-99), computed tomography, and ultrasound are generally not recommended as diagnostic modalities for pedal osteomyelitis[22] due to their low specificity and poor ability to differentiate anatomical detail.[7]

Not the Whole Story: A Problem with MRI Studies

MRI is considered the most sensitive and specific imaging modality of those commonly available, with an average sensitivity of 99% and specificity

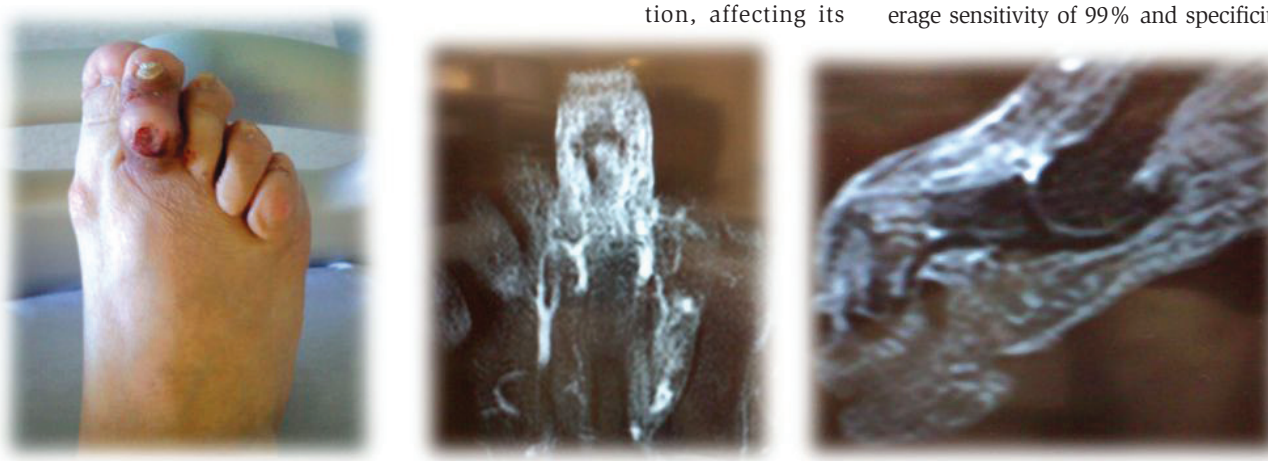


Figure 3: A chronic second digit diabetic neuropathic ulcer with reactive inflammatory bone marrow edema diagnosed as osteomyelitis by the radiologist but confirmed uninfected by surgical bone pathology and culture.

of 81%.[5,6,9,10] Yet despite this apparently high-powered ability to diagnose osteomyelitis, one must consider three major issues with this modality: the significance of bone marrow edema, the effect of prevalence on the likelihood of infection, and the shortcomings of sensitivity and specificity of MRI as reported in the research literature.

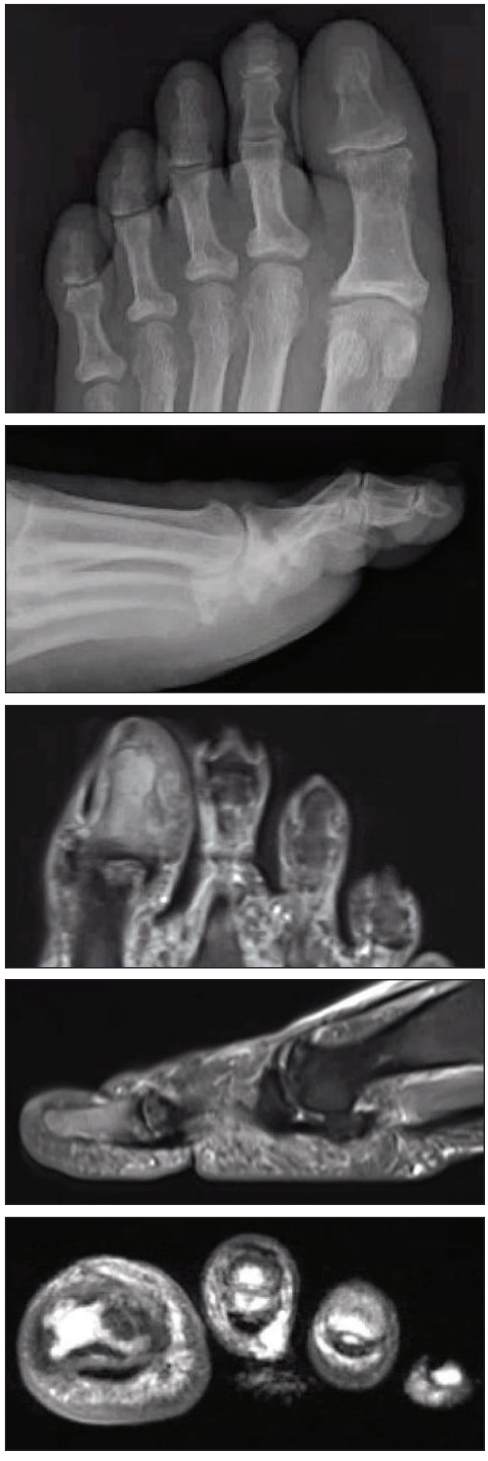


Figure 4: Radiographic and MRI images of a 65 year-old patient misdiagnosed with osteomyelitis of the distal phalanx of the hallux. Partial nail avulsion completely resolved the patient's symptoms.

Bone Marrow Edema: A Caution

Increased signal intensity on T2-weighted or STIR MRI images, demonstrating bone marrow edema, may be caused by many different factors. These include inflammation of adjacent tissues causing inflammation of the bone, Charcot neuro-arthropathy, stress fractures, acute fractures, recent surgery, arthritis, altered weight-bearing, and mechanical factors. As a result, bone marrow edema is highly nonspecific. This potential for error is exemplified by a recent study by LaFontaine, et al. Retrospectively reviewing MRI diagnosis in comparison with biopsy-proven osteomyelitis, these researchers found a 29.3% incorrect diagnosis in their cohort of 166 patients.[26]

An example of this situation is noted in Figure 3. The patient in these images suffered from a chronic dorsal second proximal interphalangeal joint ulceration that probed to bone. On admission to the hospital, an MRI was performed in which the STIR images demonstrated increased signal intensity in the soft tissue, middle phalanx, and distal aspect of the proximal phalanx of the digit. This was diagnosed as osteomyelitis by the reading radiologist. However, after surgical intervention, in which a digital arthroplasty and metatarsophalangeal joint release were performed, post-operative bone pathology and culture were negative for infection. At the eight year follow-up, this patient remained ulcer and infection-free. The cause of the increased signal uptake in the bone was due to a combination of acute soft tissue inflammation as well as chronic bone inflammation from the hammertoe deformity.

Similarly, a second misdiagnosed osteomyelitis case is represented in Figure 4. This 65 year-old patient presented to the emergency room with signs and symptoms consistent with onychocryptosis and paronychia of the left great toe.

Radiographs and MRI were obtained and both read as diagnostic of osteomyelitis of the distal phalanx of the hallux. However, after performing a nail avulsion and allowing time to heal, this patient completely resolved her symptoms with no further clinical signs of osteomyelitis.

These cases highlight the importance of a holistic approach when using MRI, including the presence of the definitive criteria discussed below.

Confluent decreased signal intensity on T2 signals is the most diagnostic of osteomyelitis on MRI studies.

What Are the Appropriate Diagnostic Signs of Osteomyelitis on MRI Imaging?

Based on the above examples, it is clear that using MRI to diagnose pedal osteomyelitis must be done with a full understanding of the important diagnostic signs (summarized in Table 1). The key diagnostic characteristic is the presence of a confluent geographic hypo-intense signal on T1-weighted images.[23] Although increased signal intensity on T2-weighted or STIR images may be easier to see—and thus more sensitive—the fat loss on the T1-weighted images is more representative of the true destructive changes of osteomyelitis.[18] Collins, et al. performed an analysis of diagnostic MRI characteristics on 80 feet with bone culture and biopsy-confirmed osteomyelitis. They found a confluent, geographic, medullary pattern of infiltration on T1-weighted MRI images to be the only characteristics present in 100% of patients. Importantly, none of the patients with a hazy, subcortical, re-

ticulated pattern on decreased T1 signal had surgically proven osteomyelitis.[4]

When considering the presence of suspected osteomyelitis, it is important to compare the signal intensity on the T1 and T2-weighted sequences. For example, increased T2 signal intensity but with normal-appearing bone on the T1 sequences is more likely to be reactive bone marrow edema than osteomyelitis.[14] It is also not necessary to order this study with contrast. Labiste and colleagues found no added value to the addition of contrast for the diagnosis of osteomyelitis in a recent systematic review.[25]

Combining a number of characteristics, including an ulcer contiguous with bone, "erasure," (cortical destruction), along with a focused consideration of the T1 and T2 image characteristics, can make the diagnosis of osteomyelitis in most cases.[8,14,23] Figure 5 demonstrates an example of appropriately considering these characteristics.

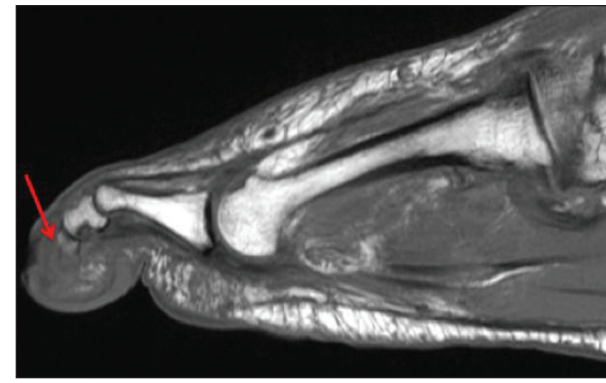


Figure 5: Patient with surgically confirmed MRI diagnosis of osteomyelitis of the second digit distal phalanx, demonstrating the characteristic confluent geographic decreased signal on T1 image with erasure sign.

Bone biopsy and culture is the gold standard for the diagnosis of osteomyelitis in the foot.

The Effect of Prevalence

One must read the current literature about any diagnostic method, including MRI, for the diagnosis of osteomyelitis, with the appropriate perspective. Most germane to this discussion is the fact that prevalence (the occurrence of a disease in a chosen population) will significantly affect the results of any diagnostic study. Those studies using hospitalized patients, who already have a higher prevalence of foot infections, are more likely to also have osteomyelitis. Similarly, those studies with low infection prevalence are less likely to have pedal osteomyelitis.

The reason for higher prevalence leading to increased diagnoses is due to selection bias. This may be understood by a simple analogy. Consider a hunter attempting to shoot down a bird flying in a flock (Figure 6). By having a large number of target options, the hunter is more likely to hit a bird. However, if there is only one bird (a low prevalence), the hunter is less likely to hit that bird. As such, a large number of patients in a study with infection (a greater prevalence) will lead to a larger number of patients with pedal osteomyelitis simply by the increased numbers. Studies, then, with high prevalence rates of osteomyelitis, as is the case with many of the studies examining MRI for the diagnosis of osteomyelitis, must be read with caution.

An important example of this concept is demonstrated by comparing the original probe-to-bone study by Grayson and colleagues[13] with that of Lavery, et al.[17] Grayson found a high 89% positive predictive value of the probe-to-bone test for the diagnosis of pedal osteomyelitis. However, this study was performed in a hospital setting on patients admitted for foot infections (a high prevalence). Lavery and colleagues, on the other hand, performed their study in an outpatient clinic with a low 12% prevalence of pedal infections, leading to a positive predictive value of only 57%. This comparison shows that the prevalence of the disease in question must be considered when determining the strength of a particular diagnostic test.

TABLE 1:

Diagnostic Signs of Pedal Osteomyelitis on MRI

***Adapted from Donovan and Schweitzer*[8,22]**

T1 confluent low signal in a geographic pattern
Ulcer contiguous with bone
Sinus tract formation
Erasure (loss of cortical integrity)
Periosteal reaction
Cellulitis
Abscess

The Shortcomings of Sensitivity and Specificity

Almost all studies examining MRI as a diagnostic modality for osteomyelitis of the foot utilize sensitivity and specificity as the primary statistical methods of reporting. However, in the case of physicians treating patients, the diagnosis is not known yet, so sensitivity and specificity are not appropriate. The reason for this is that these statistics are intended for populations and not individuals. Sensitivity and specificity are appropriate when the diagnosis is already known.[1] Research literature should thus report a different statistic.

Instead, using likelihood ratios is a more appropriate statistical reporting method. Likelihood ratios are reported as positive (+LR) or negative (-LR) and are calculated using the sensitivity and specificity statistics (Figure 7). Positive likelihood ratio is the probability of having the diagnosis with a POSTIVE test result (true positives), while negative likelihood ratio is the probability of having the diagnosis with a NEGATIVE test result (false negatives).

Simple rules of thumb can then be created to assist those reading the literature to determine the likelihood of an osteomyelitis diagnosis. A positive or negative LR greater than 10 effectively rules in the disease, while a positive or negative LR less than 0.1 rules out the diagnosis. Additionally, likelihood ratios can be combined with pre-test probability (discussed below) to determine post-test probability for a single patient (LR x Pre-test probability = Post-test probability).

Considering the statistics reported in the medical literature in this manner significantly changes how these studies would be applied to patients with suspected pedal osteomyelitis. As an example, the well-cited meta-analysis from Kapoor and colleagues examined MRI for the diagnosis of osteomyelitis. They found MRI to be 82.5% sensitive and 90% specific to diagnose this disease.[15] However, if one were to calculate the positive likelihood ratio from these statistics, one would arrive at a likelihood ratio of 8.25, which does not reach the greater than 10 limit discussed above.

Using this information combined with the pre-test probability reveals the importance of probability. At a 60% pre-test probability of osteomyelitis (relatively high), a likelihood ratio of 8.5 leads to a 95% chance the patient has osteomyelitis. But if the pre-test probability is lower, for example 10%, then there is only a 50% chance the patient has osteomyelitis. One can take from this that if a clinician has a high clinical suspicion of osteomyelitis in a patient and uses the high likelihood ratio determined from the Kapoor study, then the probability the patient actually has osteomyelitis is very high and treatment should ensue accordingly. Using likelihood ratios is an effective statistical way to convert sensitivity and specificity data into something useable for the individual patient.

In patients hospitalized with infections of the feet, prevalence of osteomyelitis is most likely high.

Figure 6: Selection bias, as a result of prevalence, changes the results of a study.

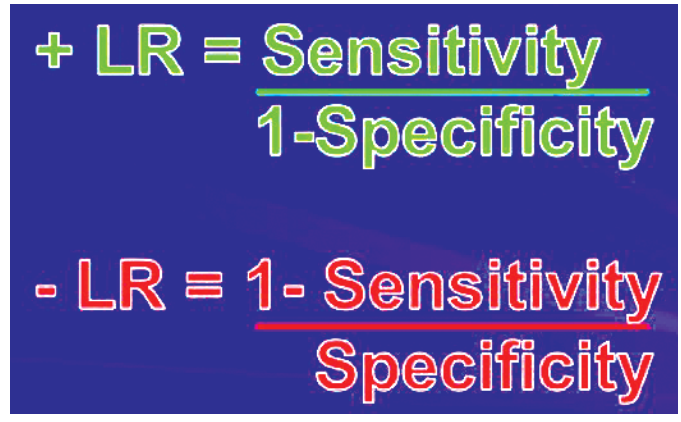


Figure 7: Calculation method to find likelihood ratios from sensitivity and specificity data.

A 3-Step Method for the Diagnosis of Pedal Osteomyelitis

Considering the above discussion and the weaknesses of relying on MRI alone as a diagnostic test, one might reasonably ask, "What is an appropriate method to diagnose pedal osteomyelitis?" A simplified 3-step method becomes a useful clinical tool to diagnose and guide treatment of pedal osteomyelitis. These three steps are summarized as follows:

1) Perform a detailed history and physical examination.

2) Consider the pre-test probability of osteomyelitis.

3) Order tests to further investigate or institute treatment.

Step 1: Information Gleaned from the History, Physical, and Laboratory Studies

Performing a detailed history and physical has always been the cornerstone of modern medical treatment, and this remains equally true for osteomyelitis of the foot. One must first recall that there are three ways in which a patient may acquire osteomyelitis. Hematogenous spread occurs when a distant infection enters the blood stream and inoculates the bone downstream of that infection. Direct inoculation osteomyelitis begins when a bacteria-carrying source outside the body enters through the skin, contaminates and then infects the bone. Contiguous spread ensues when normal skin bacterial flora enter the body through an opening such as an ulcer, proceeds deeper and then infects the bone.

It is highly important, then, for clinicians to understand that the former two methods, hematogenous spread and direct inoculation, are very rare occurrences in the foot, and hematogenous spread almost

never occurs in adult pedal osteomyelitis. It has been demonstrated that 94% to 99% of pedal osteomyelitis is associated with an ulcer.[3,18] Based on this information, the astute clinician will understand that patients who present with signs of a foot infection (erythema, edema, pain, and warmth) but lack a visible wound, callus, fissure, or other skin entry have a different diagnosis, such as Charcot neuro-arthropathy. However, one must be cautious relying entirely on clinical experience because it has been shown that underlying osteomyelitis may be "clinically silent".[21] An early study found that only 32% of osteomyelitis confirmed by bone biopsy and culture had been diagnosed clinically.[21]

However, more recent research has emphasized the improved diagnostic power of combining clinical judgment with certain diagnostic tests. The addition of these clinical and laboratory tests provides potentially important information when making the diagnosis of osteomyelitis. Ertugrul, et al. found that an ulcer size greater than 2 cm2 with a serum erythrocyte sedimentation rate (ESR) greater than 65 mm/hr had a sensitivity of 83%, sensitivity of 77%, positive predictive value of 80%, and negative predictive value of 81%.[11] Calculating the more useful likelihood ratios, one sees a positive likelihood ratio (LR) of 3.6 and negative LR of 0.22. With this information one can rule out but not rule in osteomyelitis.

Fleisher and colleagues similarly looked at various characteristics that would be assistive in diagnosing osteomyelitis. Using a case control experimental model, these researchers studied clinical and laboratory methods for the diagnosis of pedal osteomyelitis in 54 patients. They found combining clinical and serologic testing had a higher sensitivity and specificity for osteomyelitis than any single test. Specifically, an ulcer depth greater than 3mm combined with either a C-reactive protein (CRP) greater than 3.2 or ESR greater than 60mm/hr had a sensitivity of 100% and specificity of 60% and 55%, respectively.[12]

A discussion of the clinical diagnosis of osteomyelitis must include the probe to bone test; and in 2016, Lam and colleagues performed a systematic review to determine the accuracy of this test.[16] Pooled values from the seven included studies found the following: sensitivity 0.78, specificity 0.83, positive predictive value 0.91, and negative predictive value 0.84. It is important to understand that in all of the included studies but one, the prevalence of osteomyelitis was moderate to high (0.62—0.80) with a pooled prevalence of 0.59.

The likelihood ratio allows determination of post-test probability for a single patient.

More importantly, this study yields a positive likelihood ratio of 5.11 and negative likelihood ratio of 0.16. From this data, one can state that in a patient with possible osteomyelitis who is part of a group with high prevalence, there is a five-fold chance of a true positive diagnosis but a much higher chance of ruling out osteomyelitis if these results are negative.

In summary, information that should be considered from the history, physical, and laboratory studies include the presence of an ulcer in a patient with high infection prevalence (such as hospitalized patients with acute infection), an ulcer size greater than 2 cm2, depth greater than 3 mm, and positive probe to bone should increase one's clinical suspicion of osteomyelitis. Addition of a CRP greater than 3.2 and/or an ESR greater than 60mm/hr increases the likelihood more yet (Table 2).

TABLE 2:

Characteristics Assistive in Estimating Pre-test Probability of Pedal Osteomyelitis[12,21]

Low Pre-test Probability (<50%)	Moderate to High Pre-test Probability (>50%)
• Acute ulcer	• Deep ulcer
• Shallow ulcer	• Recurrent ulcer
• Mild infection	• Multiple ulcers
• Negative probe to bone	• Bone exposed
• Rapid improvement	• High SED rate, CRP
• Healed ulcer	• Erosions on radiographs
• Lack of deformity	
• Low ESR, CRP	
• Absent radiographic findings	

Step 2: Using Pre-test Probability

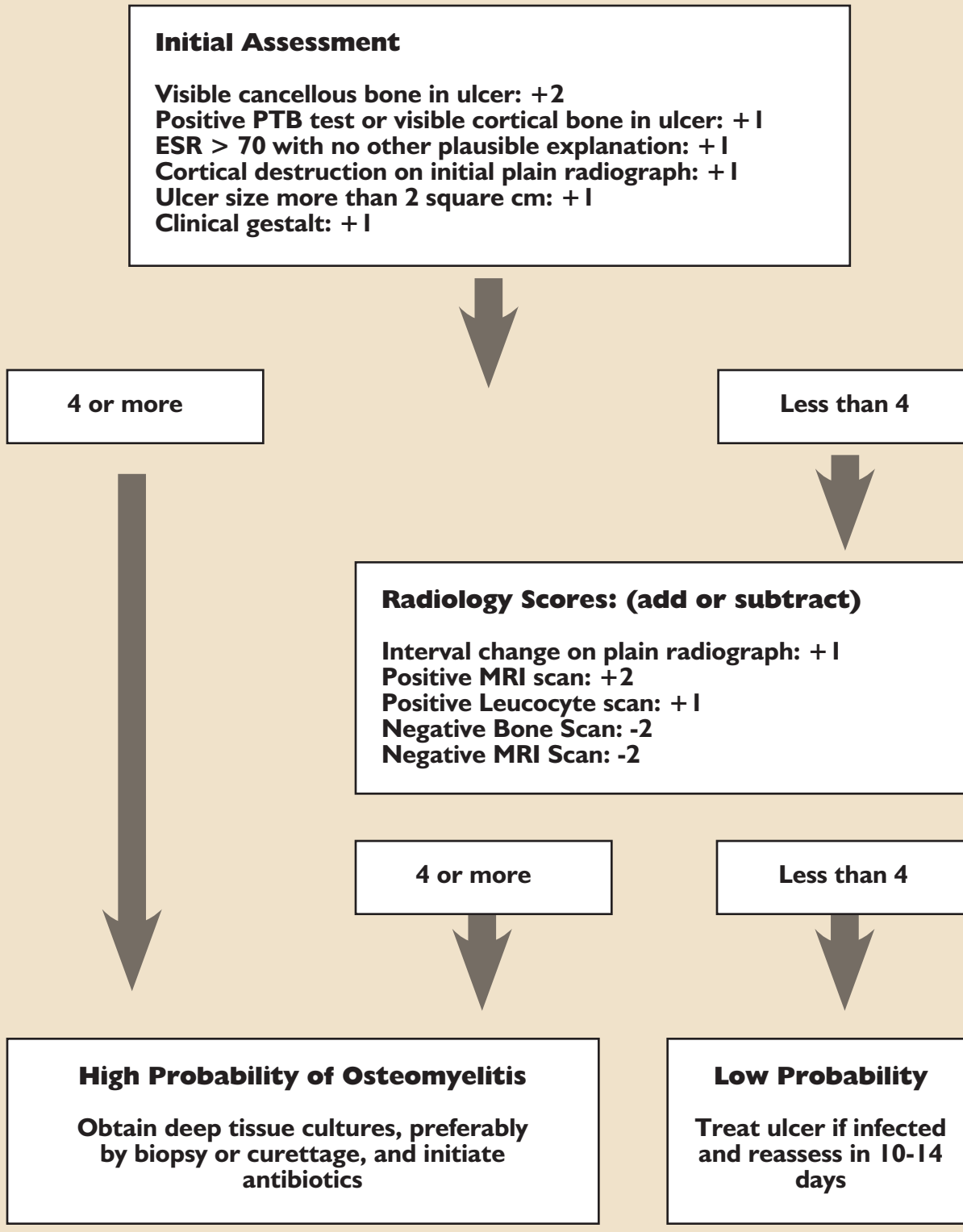
The next step in the process is to consider the pre-test probability. Pre-test probability is generally estimated in one of three ways: using one's clinical experience, estimating the prevalence in the population, and using published clinical prediction rules.

Clinical Experience and Pre-test Probability

In clinical practice, it is often necessary for physicians to estimate pre-test probability. The information

FIGURE 8:

A Modern Evidence-Based Clinical Prediction Rules System



in Table 2 is helpful to determine a low versus moderate/high pre-test probability.

Very few studies have examined the true prevalence of pedal osteomyelitis. However, Newman and colleagues found a prevalence of 68% using bone biopsy and culture in a cohort of 41 diabetic foot ulcers.[21]

In light of clinical uncertainty, recent researchers have attempted to create clinical prediction rules. Markanday used a 4-point threshold rule system to determine the probability of pedal osteomyelitis, which guides treatment (Figure 8). This early clinical prediction rule is a useful algorithm but remains to be validated.[20]

biopsy and culture to be a mainstay of diagnosis of pedal osteomyelitis.

Final Thoughts on the Original Case

Returning to the original case introduced at the beginning with clinical and radiographic images shown in figures 1 and 2, the next step in evaluation is to determine if this 65 year-old male with infection has osteomyelitis. Important information from the history and physical include a recurrent ulceration that probes to periosteum (2 cm depth) in a patient with peripheral arterial disease. Laboratory studies demonstrated an ESR of 73 mm/hr and CRP 10.6. This patient should be considered to have a high probability of osteomyelitis even before any advanced imaging is performed. In this case, an MRI provides little new information, and a percutaneous or limited open bone biopsy for histopathology and culture would both confirm the diagnosis and guide antimicrobial treatment.

Exposed bone leads to a high pre-test probability of pedal osteomyelitis.

Step 3: Order Further Tests or Begin Treatment

Based on a synthesis of the above information, clinicians should determine whether more testing is needed or treatment may begin immediately. For those patients with a very low probability of osteomyelitis, observation and treatment of the major diagnosis may proceed. In the case where a high probability of pedal osteomyelitis is evident, the clinician may move immediately to treatment, be that surgery, antimicrobial treatment, or a combination thereof.

The more important aspect of this algorithm is for those patients in which a diagnosis of osteomyelitis is of intermediate probability, i.e., uncertain. In these cases, further testing is necessary. This includes advanced imaging such as MRI, surgical biopsy and culture, or, in the case of less emergent situations, watchful waiting with serial radiographs. One must keep in mind, though, that all of the major characteristics of osteomyelitis (not only bone marrow edema) must be present on MRI for a presumptive diagnosis to be made.

Given the potential for a false diagnosis with imaging, plus the utility of bone biopsy and culture to guide future therapy, the podiatric physician and surgeon should consider

In conclusion, a negative MRI is accurate to rule out osteomyelitis, but a positive MRI should be interpreted with caution. Clinicians should consider the underlying prevalence of disease to determine the pre-test probability when making clinical decisions. Gathering all of the information from the history and physical, laboratory studies, and imaging provides relatively strong evidence on which to base decisions, with advanced imaging such as MRI to be used in uncertain cases. Finally, bone biopsy and cultures remain the gold standard and should be liberally used when indicated. **PM**

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CME EXAMINATION

1) Radiographs are NOT the most sensitive imaging method to diagnose osteomyelitis for which of the following reasons?

- **A) Excellent anatomical detail**
- **B) Changes lag behind the clinical course**
- **C) Very expensive to acquire**
- **D) Lack of availability in practice**

2) Which of the following imaging methods is the most sensitive and specific?

- **A) Computed tomography**
- **B) Scintigraphy**
- **C) Magnetic resonance imaging**
- **D) Ultrasound**

3) Which of the following is MOST diagnostic of osteomyelitis on MRI studies?

- **A) Increased T2 signal intensity in bone**
- **B) Soft tissue edema**
- **C) Confluent decreased signal intensity on T2 signals**
- **D) Bone marrow edema**

4) While viewing an MRI, increased signal intensity of the bone is noted on the T2-weighted images while the T1-weighted images are normal in appearance. Which of the following is the correct interpretation?

- **A) Diagnostic of osteomyelitis**
- **B) Reactive bone marrow edema**
- **C) Abscess formation**
- **D) No conclusion is possible.**

5) Which of the following are diagnostic signs of pedal osteomyelitis?

- **A) T1 confluent low signal in a geographic pattern**
- **B) Ulcer contiguous with bone**
- **C) Erasure**
- **D) All of the above**

6) Which of the following is the gold standard for the diagnosis of osteomyelitis in the foot?

- **A) MRI**
- **B) Radiographs**
- **C) Bone biopsy and culture**
- **D) Clinical judgment**

7) In patients hospitalized with infections of the feet, prevalence of osteomyelitis is most likely

- **A) High**
- **B) Moderate**
- **C) Low**
- **D) Absent**

Continuing Medical Education

CME EXAMINATION

8) Which of the following is a better statistical method to report imaging study success in diagnosing osteomyelitis because it allows determination of post-test probability for a single patient?

A) Likelihood ratio
B) P value
C) Sensitivity
D) Specificity

9) Which of the following characteristics leads to a high pre-test probability of pedal osteomyelitis?

A) Shallow ulcer
B) Mild infection
C) Exposed bone
D) Lack of deformity

10) A 54 year-old female is seen for evaluation of an ulcer on the plantar aspect of the first metatarsal head. The wound has been present for 2 days, is 1 mm deep, and does not probe to bone. Her ESR is 20 and radiographs do not show cortical disruption. Which of the following is the most likely conclusion?

A) This patient has osteomyelitis.
B) This patient has an abscess.
C) Treat with intravenous antibiotics.
D) Treat with debridement and off-weighting.

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EXAM #7/22
Radiographic Evaluation of Infection: An Update (Shapiro)

Circle:

1.	A	B	C	D	6.	A	B	C	D
2.	A	B	C	D	7.	A	B	C	D
3.	A	B	C	D	8.	A	B	C	D
4.	A	B	C	D	9.	A	B	C	D
5.	A	B	C	D	10.	A	B	C	D

Medical Education Lesson Evaluation

Strongly agree [5]	Agree [4]	Neutral [3]	Disagree [2]	Strongly disagree [1]

1) This CME lesson was helpful to my practice ____

2) The educational objectives were accomplished ____

3) I will apply the knowledge I learned from this lesson ____

4) I will makes changes in my practice behavior based on this lesson ____

5) This lesson presented quality information with adequate current references ____

6) What overall grade would you assign this lesson?

A B C D

7) This activity was balanced and free of commercial bias.

Yes _____ No _____

8) What overall grade would you assign to the overall management of this activity?

A B C D

How long did it take you to complete this lesson?

_____hour _____minutes

What topics would you like to see in future CME lessons ? Please list :

_____

_____

_____

_____

_____