Osteomyelitis and Lower Extremity Amputations in the Diabetic Population

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Abstract:

Osteomyelitis, ulcers, and foot infection play an integral role in the causal pathways leading to minor and major lower extremity amputations in persons with diabetes mellitus. We herein present a literature review detailing the etiology of diabetic foot osteomyelitis, its diagnosis, and suggested treatments.

Key words: Osteomyelitis, amputation, diabetes mellitus, diabetic ulcer, diabetic foot.

Introduction

Infection of bone (osteomyelitis) in and of itself has long been the culminating event leading to many non-traumatic lower extremity amputations. However, in the diabetic population osteomyelitis has emerged as one of the dominant complications of long standing diabetic foot ulcers. Reports have indicated that diabetic persons have approximately a 15% lifetime risk of developing a pedal ulceration.⁴-⁶ Although this percentage may seem acceptable, as the incidence of diabetes swells and the sentinel age at which even type 2 diabetes mellitus is being diagnosed plummets, the numbers become epidemic in proportion. In the presence of a pedal ulceration upwards of 66% of those open wounds will result in infection of the underlying bone by contiguous spread from soft tissues in the face of severe infection.⁴ Severe infection aside, osteomyelitis prevalence in diabetic foot ulcers ranges from 10-20%.⁵,⁶

The mere presence of osteomyelitis significantly increases the individual’s chance of lower extremity amputation.⁷,⁸ The high incidence of osteomyelitis in diabetic foot wounds easily makes it an important cause of non-traumatic lower extremity amputations wherein diabetes accounts for approximately 60% of such amputations.⁹ The morbidity, mortality, and costs of diabetic lower extremity wounds alone can be overwhelming, but when coupled with the sequelae of osteomyelitis-related amputations the burden is increased exponentially.

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Etiology of Osteomyelitis

Diabetes coupled with neuropathy sets the stage for the development of foot ulcerations. These pathognomonic lesions are most common in areas of increased pressure including the first and fifth metatarsal heads and calcaneus, as well as areas predisposed to repetitive trauma such as the tips of the toes. Ischemic lower extremity changes can complicate the recovery period and contribute to delayed or non-healing of the wounds. Diabetic immunopathy also increases the risk of soft tissue infection during this time.

The loss of the intact epithelium predisposes the underlying bone to infection by direct inoculation. Microorganisms express adhesion factors for the bone matrix and begin by invasion of the cortical bone. Once the cortical bone barrier is breached the microorganism is free to spread within the bone by vascular Haversion channels within the osseous structure. Soon, medullary bone and marrow are affected and hasten the spread of pathogens to non-localized areas. Pockets of bone necrosis (sequestra) ensue, triggering the proliferation of osteoblasts and new bone formation in a haphazard fashion. This results in the classic radiographic sign of involucrum.

Although diabetic foot infections are generally polymicrobial in nature, osteomyelitis most often involves a single pathogen. Staphylococcus aureus and coagulase negative staphylococci account for approximately 70-80% of such infections.11,12

Diagnosing Osteomyelitis

Bone biopsy has long been considered the gold standard for diagnosing osteomyelitis, but in most cases is not obtained due to concern over inoculating non-infected bone in a non-surgical setting. Most practitioners therefore currently rely on clinical findings and ancillary testing. Non-healing ulcerations present for greater than 4 weeks duration13 and greater than 2cm² in size have been associated with increased rates of osteomyelitis.8,14

Bone visible within the wound base or positive probing to bone through the ulceration site with a sterile stainless steel probe are also highly indicative of osteomyelitis with positive predictive values of 57% and 89% respectively.4-6

When clinical suspicion of osteomyelitis is strong and further diagnostic evidence is needed, ancillary testing is employed. This includes plain radiographs, technetium scans, indium labeled leukocyte scans, and MRI.15-28 Incorporating current evidence and concepts in this regard, an algorithm for diagnosing osteomyelitis underlying chronic diabetic foot wounds is presented in Figure 1.

Plain radiographs:

Evidence of osteomyelitis on X-rays includes periosteal reaction, sequestrum, involucrum and gross osseous destruction. Caution should be employed with X-ray interpretation as radiological changes may lag actual induction of osteomyelitis by as much as 10-14 days.15 Charcot arthropathy should be considered as a differential diagnosis and may distort the diagnosis of osteomyelitis when present. Radiographs are however useful and inexpensive when monitoring the progression of osteomyelitis once pathognomonic findings are visible.

Technetium Bone Scan:

Osteomyelitis can be seen as increased focal bony uptake of the technetium at the area of interest on delayed images (3rd phase). (Figure 2) Although highly sensitive for osteomyelitis, bone scans convey very little specificity for osteomyelitis.15,16 Due to its high sensitivity, lack of uptake at the bone adjacent to the ulceration on three phase bone scans is definitive for the absence of osteomyelitis. Nonetheless, false negatives may occur in patients with vascular insufficiency of the lower extremities.
Clinical Suspicion for Osteomyelitis

- **Radiographs**
  - Negative(-)
  - Positive(+) (periosteal rxn, cortical erosion)

  - Local wound care & repeat x-rays 2-4 weeks
    - Positive(+)
    - Negative(-) → Wound area decreasing; no bone exposed
      - Osteomyelitis
      - No change in wound area in 4 weeks; Osteomyelitis doubtful
        - +/- probe to bone
          - Technetium Bone Scan
            - Positive(+)
            - Negative(-) → No osteomyelitis

          - Bone Biopsy or
            - MRI or
              - inflammatory process present such as postsurgical changes or acute Charcot
                - Positive(+)
                  - (beware of false(-) on abx)

                    - Osteomyelitis

          - Positive(+)
            - (↑ signal intensity on T2 image at the osseous level)

            - Combine with Indium labeled leukocyte scan
              - Both Positive(+)
                - (beware of false +)

                    - Osteomyelitis

**Figure 1** Algorithm for diagnosis of osteomyelitis underlying a chronic wound. (*modified from ref. 28; Hartemann-Heurtier A, Senneville E, 2008*)
Indium labeled leukocyte scan:

This test is capable of identifying an infectious process in the area of interest, but due to poor spatial resolution it is often difficult to differentiate activity between soft tissues or osseous structures involved. Leukocyte scanning in combination with technetium scans are quite accurate with both sensitivity and specificity of approximately 90%.\textsuperscript{17,18} False negative results for both technetium and leukocyte scanning can be found in the presence of severe PAD wherein the isotopes might not be able to localize in the suspected sites of involvement.

MRI:

MRI is the single most useful test in diagnosing osteomyelitis although it is expensive.\textsuperscript{7,10} Findings of osteomyelitis appear as increased signal intensity on T2 weighted or fat suppressed images indicating fluid replacement or inflammation. (Figure 3)

Sensitivity and specificity of MRI to detect osteomyelitis is similar to that of bone and leukocyte scanning combined, 90% and 70-80% respectively.\textsuperscript{19,20} MRI is also valuable in visualizing the extent of osteomyelitis and assisting with surgical planning. Contraindications include retained metal implants in the area of interest that cause distortion of the resulting image.

Dinh et al performed a meta-analysis of the accuracy of diagnostic tests for the diabetic patient and reviewed a total of nine studies pertaining to the topic. A summary of their findings are contained in Tables 1 and 2.\textsuperscript{21}

\textbf{Treatment of Osteomyelitis}

The choice of conservative vs. surgical treatment of osteomyelitis has been debated for years. Historically, definitive treatment of osteomyelitis has been by thorough excision of affected bone followed by several weeks of antibiotic therapy. Recent studies have investigated conservative treatments with long term oral or parenteral antibiotics with promising results.
Table 1  Summary statistic of imaging modalities in diagnosing diabetic osteomyelitis (After Dinh\textsuperscript{21}).

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>Studies</th>
<th>Sample Size</th>
<th>Size</th>
<th>Sensitivity (95% CI)</th>
<th>P-value</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe to bone</td>
<td>7, 14</td>
<td>288</td>
<td></td>
<td>0.60</td>
<td>&lt;.001</td>
<td>0.91</td>
</tr>
<tr>
<td>Radiographs</td>
<td>14, 22-24</td>
<td>177</td>
<td></td>
<td>0.54</td>
<td>.006</td>
<td>0.68</td>
</tr>
<tr>
<td>MRI</td>
<td>18, 22, 23, 25</td>
<td>135</td>
<td></td>
<td>0.90</td>
<td>&lt;.001</td>
<td>0.79</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>14, 22-24, 26, 27</td>
<td>185</td>
<td></td>
<td>0.81</td>
<td>&lt;.001</td>
<td>0.28</td>
</tr>
<tr>
<td>WBC Scan</td>
<td>14, 18, 24, 25, 27</td>
<td>269</td>
<td></td>
<td>0.74</td>
<td>&lt;.001</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Table 2  Accuracy of clinical & imaging techniques for diagnosing osteomyelitis (After Dinh\textsuperscript{21}).

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>Studies</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probe to bone</td>
<td>7, 14</td>
<td>49.45</td>
</tr>
<tr>
<td>Radiographs</td>
<td>14, 22, 23, 24</td>
<td>2.84</td>
</tr>
<tr>
<td>MRI</td>
<td>18, 22, 23, 25</td>
<td>24.36</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>14, 22, 23, 24, 26, 27</td>
<td>2.10</td>
</tr>
<tr>
<td>WBC Scan</td>
<td>14, 18, 24, 25, 26, 27</td>
<td>10.07</td>
</tr>
</tbody>
</table>

However, early limitations to these studies included lack of power as well as lack of reliable bone cultures and histopathological confirmation of osteomyelitis. Recent studies investigating non-surgical treatment of osteomyelitis have achieved both, and have been shown to arrest osteomyelitis in 80.5% and 82.3% of patients respectively.\textsuperscript{29,30,31} In these studies and others however, use of oral and IV antibiotics were interchanged at inconsistent periods of time and duration of treatment varied widely ranging from 3 weeks to 24 months.

In an attempt to gain some ground on the debate, Berendt et al\textsuperscript{29} reviewed 19 articles reporting treatment of osteomyelitis with conservative vs. surgical treatment and combinations of both.\textsuperscript{30-49} Results of this study revealed comparable rates of osteomyelitis arrest for both surgical and medically treated patients. He was unable to uncover any controlled studies that directly compared outcomes of antibiotic therapy alone vs. surgical treatment followed by antibiotic therapy.

Jeffcoate et al also reviewed 11 articles reporting primarily medical management of osteomyelitis with limited surgical intervention and found similar results; remission rates of osteomyelitis varying from 29%-88% with the total number of reported patients treated with conservative care to be in excess of 500 as of 2004.\textsuperscript{50}

**Amputations**

Surgical treatment of osteomyelitis should be employed in cases of failed conservative treatment and as primary treatment of diabetic osteomyelitis in patients with severe limb or life threatening infections. Such procedures include partial resection of infected bone, partial foot amputations, major limb amputations, or open guillotine amputation for acute necrotizing infections in an attempt to reduce mortality. (Figure 4) Increased healing rates and decreased length of antibiotic treatment have been reported with early surgical intervention as compared to medical treatment alone for osteomyelitis.\textsuperscript{37}
When considering amputation for treatment of osteomyelitis the surgeon must consider many factors when determining the type and level of amputation. Such considerations include whether the amputation is performed *emergently* to control infection or if *curative* for the resolution of chronic osteomyelitis. Secondly, adequate resection of infected bone needs to be assured. Resection of bone with greater than 5mm of clear margins has been associated with decreased rates of osteomyelitis reoccurrence. Third, thought must be given to the preservation of a functional limb post-operatively.

The American College of Foot and Ankle Surgeons (ACFAS) has developed guidelines that should be considered when selecting amputation levels:

a) Creation of a distal stump that is durable and resistant to pressure breakdown.

b) Creation of a distal stump that can be easily accommodated with shoe gear, orthotic device, or prosthesis.

c) Creation of a distal stump that will not cause muscle or other dynamic imbalances.

d) Healing by primary intention if possible.

Treatment of diabetic foot osteomyelitis can be complicated by the presence of lower extremity ischemia. Persons with diabetes are seven times more likely to suffer a lower extremity amputation than non-diabetics.
The patient’s vascular status plays a crucial role in determining the level of amputation. Since morbidity and mortality is greatly increased with more proximal amputation, aggressive revascularization should be performed on suitable surgical candidates prior to definitive amputation procedures for the resolution of osteomyelitis. Sheahan et al reported that patients who underwent revascularization following minor foot amputation had significantly increased limb loss as compared to patients that underwent vascular intervention prior to amputation.

**Conclusion**

Diagnosis and treatment of osteomyelitis requires a multi-disciplinary approach. Due to the large numbers of diabetic lower extremity ulcers that progress to osteomyelitis and the significant morbidity and mortality related to the sequela of diabetic foot osteomyelitis, appropriate diagnosis and treatment is essential. When strong clinical suspicion of osteomyelitis exists, systematic ancillary testing should be performed to confirm the presence of bone infection. Many imaging tests exist for diagnosing osteomyelitis. Sensitivity, specificity and limitations of any test employed should be well known. Treatment of osteomyelitis may be either primarily medical, surgical or a combination of both. Although little research in the area of surgical management of osteomyelitis exists, the traditional approach to eradication of osteomyelitis has been through surgical resection of infected bone combined with limited antibiotic therapy. Recent studies have produced acceptable rates of osteomyelitis remission with conservative or medical treatment. However these studies are flawed and have employed a myriad of methods and durations of antibiotic treatment. Medical treatment of osteomyelitis should be culture directed based on needle puncture or bone biopsy specimens that have been accurately collected.

Antibiotic therapy should target the major pathogens of osteomyelitis including staphylococcus aureus and coagulase negative staphylococci. Appropriate lower extremity amputations should be reserved for cases of failed conservative therapy, when treating severe limb threatening infections, and when simple local resection of osteomyelitis is not deemed feasible.

Unfortunately, there is still no definitive treatment regimen that consistently yields success in the treatment of osteomyelitis. Randomized controlled trials need to be undertaken in the pursuit of discovering the “gold standard” for the treatment of osteomyelitis with particular interest in the diabetic population.

**References**


