



eInfections Review: VOLUME 2, NUMBER 9

Osteomyelitis/Diabetic Foot Infections

In this Issue...

Diabetic foot infections and the ensuing osteomyelitis are common occurrences among persons with diabetes, and many patients eventually require amputation. Health care costs associated with managing diabetic foot ulcers are quite high. Additionally, the indirect costs, in terms of disability and overall economic impact, overshadow the direct medical costs.

Because of the polymicrobial nature of many of the wounds and their association with osteomyelitis, antibiotic selection is challenging. It is often unclear which organisms are commensal and which are pathogenic. In this issue, we review the microbiology of diabetic wound infections and osteomyelitis, the importance of appropriate bone sampling, the radiographic modalities for diagnosis, and current controversies in treatment.



Program Information

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Length of Activity

1 hour

Release Date

July 8, 2010

Expiration Date

July 7, 2012

Next Issue

August 3, 2010

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Review the microbiology of chronic diabetic wound infections and osteomyelitis.
- Review the diagnostic modalities used to define osteomyelitis and diabetic wounds, including the role radiology and nuclear medicine.
- Develop an evidence-based approach to treating and managing osteomyelitis and chronic wounds.

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- **Sara E. Cosgrove, MD, MS** – has disclosed that she has received grants or research support from Cubist, AdvanDX, and Astellas, and served as a consultant for Theravance/Astellas, Merck, and Forest.

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Kristine E. Johnson, MD, has disclosed she has received grants or research support from BMS, has also served as a consultant for LifeCell.

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COMMENTARY

It has been estimated that approximately 15% to 25% of patients with diabetes will develop a diabetic foot ulcer at some point.¹ Among these individuals, 14% to 24% will experience soft tissue infection, undergo an amputation for osteomyelitis, or both.¹ Health care costs associated with diabetic foot ulcers are enormous, with treatment of these wounds accounting for 20% to 25% of all hospitalizations among persons who have diabetes.²

The combination of diabetic peripheral neuropathy and small-vessel arterial disease places persons with diabetes at high risk for foot ulcers and osteomyelitis, affecting in particular the phalangeal, metatarsal, and tarsal bones. Primary prevention and foot care should be integrated into all aspects of diabetes care. Aggressive management of wounds and recognition of signs of osteomyelitis through careful physical examination and radiographic studies³ may lead to earlier intervention (surgical or nonsurgical) that might prevent progression and limb loss.^{4,5} Such wounds are often polymicrobial on tissue or swab culture, and identifying pathogen(s) vs. commensal colonizers is difficult. Greater numbers of bacterial isolates correlate with an increased risk for local infection.⁶ Bacteria cultured from superficial samples vary from deep tissue or bone culture results, and the relative "bioburden"⁷ of the wound may be associated with clinical outcomes, although this has not been well defined. The microbiome of diabetic foot wounds is more diverse, including prominent populations of anaerobes, and does not appear to be influenced by flora on the normal host skin.^{8,9}

Selecting antibiotics for treating diabetic osteomyelitis is a daunting task because of the difficulties associated with determining the causative organism(s). Bone biopsy is considered the gold standard for identifying pathogen(s). Biopsy with the incision away from the ulcer site is ideal, as little correlation has been demonstrated between bone biopsy and superficial swab cultures.⁵ In the absence of reliable biopsy data, the Infectious Diseases Society of America's guidelines suggest broad-spectrum coverage for gram-negative (including *Pseudomonas aeruginosa*), anaerobic, and gram-positive organisms (including methicillin-resistant *Staphylococcus aureus* [MRSA]).¹⁰ Anaerobes are particularly prevalent in diabetic osteomyelitis and are often difficult to culture under routine circumstances. For high tissue concentration, intravenous (IV) rather than oral antibiotics are recommended for osteomyelitis, although orally administered agents have been used successfully.^{5,11} Prolonged courses of 6 to 8 weeks are suggested. Unfortunately, no tests or radiologic studies define cure, but reimaging is reassuring if bony abnormalities resolve.

Physical examination findings and radiographic studies are key to appropriate diagnosis. The bedside probe-to-bone test is specific for osteomyelitis (pooled specificity=0.91; 95% confidence interval [CI], 0.86 to 0.94)³. If the probe-to-bone test is positive, additional studies are probably unnecessary; however, radiography helps to define the extent of infection. The presence of acute soft tissue infection, ischemia, and necrosis is of concern. Although magnetic resonance imaging (MRI) is the most sensitive and specific modality,³ nuclear medicine scans (triple-phase and leukocyte scans) can be useful as well. It is reasonable to begin with plain x-rays. However, as these films are neither sensitive nor specific, workup should advance to more sophisticated studies (MRI or nuclear medicine scans) if suspicion is high.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are useful inflammatory markers to follow with respect to therapeutic response. Treatment beyond 8 weeks to achieve normal inflammatory markers is reasonable in some settings. However, in patients with poorly controlled diabetes, the ESR and CRP may be elevated in the absence of osteomyelitis, and autoimmune disease or occult infection (i.e., central line infection) should be considered in those receiving long-term IV antibiotic therapy when these inflammatory markers remain elevated despite targeted treatment for osteomyelitis. Although not common practice, it can be useful to reimage a patient before discontinuing antibiotics and evaluate the patient's response.

The greatest debate in the approach to treating osteomyelitis of the distal lower extremity is whether to treat conservatively with antibiotics or to pursue prompt surgical



debridement accompanied by antibiotics (with possible amputation). Data are inconsistent and suggest similar success rates (approximately 50%),^{4,5} with either approach. The lack of randomized, controlled trials that address this issue provides little compelling evidence for selecting one approach over another. However, in the absence of toxicity, active gangrene, or frankly necrotic tissue, initial treatment with antibiotics provides a chance for limb salvage. If MRSA or multidrug-resistant gram-negative organisms are present, long-term IV therapy may be necessary, but that has its own inherent risks.

In summary, the diagnostic and treatment approach to osteomyelitis must be tailored to the individual patient. Since osteomyelitis can be elusive on plain film, negative initial studies should prompt additional workup. Moreover, new laboratory techniques have shown that the bacterial flora of chronic wounds is far more complex than previously thought, suggesting that anaerobes as well as *S. aureus* may play a significant role in soft tissue infection and osteomyelitis. Where at all possible, bone biopsy should be obtained to guide antibiotic selection. Although osteomyelitis is a common condition, evidence is lacking about superior antibiotic combinations, timing of debridement, and the utility of cultures. Additional prospective studies of new technologies to speed prompt diagnosis and targeted antibiotic and surgical treatment are warranted.

Take-Home Points

- Diabetic foot wounds are frequently associated with osteomyelitis and delayed healing.
- Diagnostic approach: Physical examination, revealing a positive probe-to-bone test, is highly suggestive of osteomyelitis; MRI is the preferred imaging modality.
- Microbiology: Wound cultures are frequently polymicrobial in nature but do not correlate well with bone cultures. In the absence of a bone culture, gram-negatives, anaerobes, and resistant gram-positives (MRSA in particular) should be considered with antibiotic selection.
- Treatment approach: Early surgical vs. conservative antibiotic therapy first for diabetic wound osteomyelitis is controversial. In the absence of necrotic soft tissue infection that warrants debridement, it is reasonable to attempt a course of antibiotic therapy initially.
 - Oral antibiotics appear to be equally effective for treating staphylococcal osteomyelitis compared with IV regimens.
- Staphylococcal osteomyelitis is most often methicillin-sensitive *S. aureus* (MSSA), rather than MRSA. This should help to guide antibiotic selection when reliable culture data are available.

Commentary References

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DEFINING THE MICROBIOME OF CHRONIC WOUNDS

Gontcharova V, Youn E, Sun Y, Wolcott RD, Dowd SE. **A comparison of bacterial composition in diabetic ulcers and contralateral intact skin**. *Open Microbiol J*. 2010;4:8-19.

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According to the study by Gontcharova and coworkers, conventional cultures do not adequately describe the microbial populations of chronic wounds. The goal of this study was to identify the microbial community (microbiome) that may be shared across chronic wounds compared with intact skin using 16s ribosomal DNA techniques. Many anaerobic bacteria are not isolated even when routine anaerobic collection techniques are used. As a culture-independent technique, the use of 16s ribosomal DNA (highly conserved across bacterial species and absent from animal cells) allows genus- and species-level identification of cultivable and noncultivable bacteria.

The authors collected wound debridement and skin swab samples from diabetic patients who had chronic wounds and were receiving treatment at a regional wound care center. DNA extracted from the samples underwent bacterial amplicon pyrosequencing. More than 93,000 sequences across all wounds were studied. Comparing wound and intact skin samples, the data were analyzed using a receiver-operating characteristic curve to determine the bacteria that most and least discriminated between healthy skin and wounds. Similarity and variability among bacterial populations in wounds and intact skin were evaluated using Pearson's correlation and Principal Component Analysis.

The bacterial genus that differed the most between healthy skin and wounds was *Segetibacter*. Using area under the curve analysis, all bacteria shown to have discriminating capacity were found in low frequency in both healthy skin and wound tissue. The most prevalent bacterial genera in intact skin were *Pseudomonas*, *Corynebacterium*, and *Staphylococcus*. In wounds, *Corynebacterium*, *Pseudomonas*, and *Streptococcus* were the most prevalent. *Escherichia*, *Serratia*, and *Shigella* were also more common in wounds than in intact skin. Intra-individual populations had approximately the same clustering as did inter-individual comparisons, suggesting that intact and wounded skin microbiota do not influence each other in the same host. *Corynebacterium* genera were found at considerably higher levels within wounds compared with intact skin samples. Finally, *Fingoldia* and *Peptoniphilus* were among the most populous anaerobes identified in wounds.

The microbiome of intact skin differs significantly from that of wounds, but surprisingly, host factors do not appear to play a role in the microbial composition of intact vs wounded skin in a particular individual. *Corynebacterium* and *Pseudomonas* are prevalent in both intact and wounded skin, whereas *Streptococcus* is more common in wounds. Consistent with the findings of other studies, anaerobes previously not recognized are also frequently present in wounds.

Defining the role of the microbiome in the context of chronic wounds is in the early stages of development with the availability of 16s DNA amplification and pyrosequencing. This study provides a foundation for further description of the wound microenvironment and future study of protein expression. Ultimately, a key research question will be what is the role of the microbiome in inhibition of the normal healing cascade?

Although the study approach and results of the investigation are intriguing, they are compromised by a poor study design, inconsistent selection criteria, and absence of outcomes measurement. Nevertheless, despite these methodological shortcomings, the study is valuable because it outlines a new approach to defining the microbiology of chronic wounds.

 RECOMMEND TO A COLLEAGUE

 NEWSLETTER ARCHIVE

THE VALUE OF TISSUE CULTURE IN DIAGNOSIS OF OSTEOMYELITIS

Senneville E, Morant H, Descamps D, et al. **Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot.** *Clin Infect Dis.* 2009;48(7):888-893.

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The primary goal of this prospective study was to determine the intra-individual agreement in bacterial culture results among multiple tissue samples from patients with diabetic wounds and suspected osteomyelitis. Samples were collected via (1) needle puncture (away from the ulcer site); (2) transcutaneous bone biopsy (away from the ulcer site); and (3) superficial swabs of ulcers.

Of the 451 patients with diabetes who presented with foot ulcers, 31 met the study inclusion criteria. The mean number of bacterial species per positive sample was 1.32 for needle puncture specimens, 1.35 for bone biopsy specimens, and 2.51 for swab samples. The most common organisms grown from bone biopsy, in descending order, were *Staphylococcus aureus*, *Proteus mirabilis*, and *Morganella morganii*. The correlation between bone biopsy and needle puncture cultures was 23.9%, whereas the correlation between bone biopsy and swab culture results was higher, at 41.7%. When present, *S. aureus* was common across all collection methods, with a correlation of 82.3%. Coagulase-negative staphylococci did not correlate across the sample types. Other gram-positive cocci were found in low concordance among the sampling techniques, at 30.7%. Gram-negative bacilli and anaerobes were poorly correlated across intra-individual samples, at 50% and 37.5%, respectively. When comparing needle puncture and biopsy alone, *S. aureus* was poorly correlated at 46.7%, whereas gram-negative bacilli and anaerobes were even less concordant at 24% and 25%, respectively. Across all 3 sampling techniques, bacterial isolates did not correlate significantly. Of 14 patients with histopathology available, bone biopsy specimens yielded positive cultures in 6 (42.9%). Among the differences in culture results across sampling techniques, gram-negative rods (*Pseudomonas* and *Proteus* in particular) were responsible for most (76%) of the variation.

The results of this study suggest that currently available techniques for identifying the bacterial etiology of diabetic osteomyelitis are suboptimal at best. In most settings, bone biopsy is recommended as the diagnostic procedure most likely to define etiology. The authors point out that if needle puncture by itself had been used as the single sampling method, 5 patients without osteomyelitis (negative bone cultures) would have been treated unnecessarily, and 8 patients with osteomyelitis (positive bone cultures) would not have been treated. In the setting of an open wound, the finding of greater numbers of bacterial species from superficial swab samples compared with the other 2 modalities is not unexpected. Although a needle puncture would be a simpler method available to more physicians in the outpatient setting, the poor correlation of this technique with bone biopsy does not support its broader clinical application. Surgical bone biopsy away from the wound site remains the gold standard for identification of the causative organism in patients with osteomyelitis. When bone biopsy is not an option, deep tissue curettage culture, rather than swab culture, may be beneficial if it reveals drug-resistant organisms that may be pathogens, particularly MRSA and *Pseudomonas aeruginosa*. In these cases, treatment with broad-spectrum antibiotics (oral or IV, depending in part on organism sensitivities) is indicated. Finally, the ability to generalize these results is somewhat limited because of the small sample size.



DIAGNOSTIC TESTING FOR OSTEOMYELITIS

Dinh, MT, Abad CL, Safdar N. **Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers.** *Clin Infect Dis.* 2008;47(4):519-527.

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The goal of this study was to conduct a systematic review of the literature to determine the predictive value of physical examination and radiography in diagnosing osteomyelitis in patients with diabetic foot ulcers. Using the gold standard of histopathologic examination and/or bone culture, this meta-analysis synthesized results from 59 studies. Studies describing examination of the wound, ulcer size, appearance, and radiographic evaluation were included in the meta-analysis. Radiology included plain films, MRI, triple-phase bone scan, and leukocyte scan. The authors calculated the sensitivity and specificity for examination components and imaging then pooled the results into a statistical model. They calculated inter-study heterogeneity, provided a summary of study accuracy, and addressed potential bias among the studies.

The literature search yielded 917 articles, with 9 meeting review criteria. An additional 59 studies were included following a review of article references. Only 2 studies evaluated diagnostic characteristics of the physical examination, and 1 study examined ulcer characteristics predictive of osteomyelitis. From 288 pooled cases, the sensitivity of exposed bone or probe-to-bone test was 0.60 (95% CI, 0.46 to 0.73; $P < .001$), and the specificity was 0.91 (95% CI, 0.86 to 0.94; $P = .11$). The pooled odds ratio (OR) for osteomyelitis with palpable or visible bone was 49.45 (no CI or accuracy value reported). In addition, 4 studies of plain film radiographs yielded a sensitivity of 0.54 (95% CI, 0.44 to 0.63; $P = .006$) and a specificity of 0.68 (95% CI, 0.53 to 0.80; $P = .01$), with a diagnostic OR of 2.84 and low to intermediate accuracy. Evaluators were not blinded or blinding was not reported. A total of 4 prospective studies of MRI provided a sensitivity of 0.90 (95% CI, 0.82 to 0.95; $P < .001$) and a specificity 0.79 (95% CI, 0.62 to 0.91; $P = .41$), with a diagnostic OR of 24.36 and high accuracy. Evaluators were blinded or were given minimal clinical information.

For the triple-phase bone scan, 6 studies provided a sensitivity of 0.81 (95% CI, 0.73 to 0.87; $P < .001$) and a specificity of 0.28 (95% CI, 0.14 to 0.42; $P = .01$), with a diagnostic OR of 2.10 and moderate accuracy. Evaluators had minimal clinical data or blinding was not reported.

Finally, from 6 studies of leukocyte scans, the sensitivity was 0.74 (95% CI, 0.67 to 0.80; $P < .001$), the specificity was 0.28 (95% CI, 0.17 to 0.42; $P = .01$), the diagnostic OR was 10.07, and there was low to moderate accuracy. Blinding was not mentioned, or evaluators were not blinded or were given minimal clinical data.

This thorough meta-analysis provides a useful overview of the discriminatory capacity of the probe-to-bone test and available imaging modalities. The results reflect a reasonable specificity of the probe-to-bone test. The poor sensitivity reported is counterbalanced by a high discriminatory value. MRI was the best predictive modality, but the specificity of this technique is moderate, due in part to enhancement from Charcot arthropathy. An expected finding is the poor discriminatory value of x-rays. Nuclear medicine studies have improved but limited value as screening and confirmatory tests. In summary, the detection of palpable or exposed bone on examination is concerning for osteomyelitis, but the absence does not exclude the diagnosis. MRI is the best screening and confirmatory modality, with nuclear medicine studies reasonable second-choice options if MRI is not possible. Given similar prices, the use of MRI first, rather than nuclear scans, could lead to cost savings. Negative plain films do not rule out osteomyelitis, and if clinical suspicion of infection exists, additional studies should be pursued.

A correlate of this review is the finding that despite the high incidence of osteomyelitis, few well-performed studies have carefully evaluated the diagnosis, treatment, and prognosis of patients with this infection.

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TREATMENT OF OSTEOMYELITIS: ORAL VS. IV?

Euba G, Murillo O, Fernandez-Sabe N, et al. **Long-term follow-up trial of oral rifampin-cotrimoxazole combination versus intravenous cloxacillin in treatment of chronic staphylococcal osteomyelitis.** *Antimicrob Agents Chemother.* 2009;53(6):2672-2676.

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The goal of this noninferiority study was to determine whether treatment with orally administered trimethoprim/sulfamethoxazole (TMP/SMX) for 8 weeks could achieve similar rates of success in patients with nonaxial osteomyelitis due to MSSA compared with the use of IV cloxacillin for 6 weeks, followed by oral cloxacillin for 2 weeks. Diagnostic criteria included inflammatory signs and/or sinus drainage for ≥ 10 days, x-ray results consistent with osteomyelitis, and the presence of necrotic bone. Patients with prosthetic joint infections, polymicrobial culture results, or MRSA were excluded from the study. Follow-up occurred at a minimum of 1 year after completion of therapy. The primary outcome of the study was cure rate, which was defined as symptom cessation and no relapse, such as local inflammation or sinus tract drainage. Patients with orthopedic implants at the time of diagnosis were included in the study. Blinding was not discussed.

Plachouras and colleagues aimed to characterize the PK parameters of colistin in a population of critically ill patients with MDR gram-negative infections. The investigators administered the intravenous form of colistin methanesulfonate (CMS) at a dose of 3 million units every 8 hours, measured plasma CMS and colistin concentrations, and performed population PK analysis. In the second study, Roberts and colleagues aimed to compare plasma and subcutaneous tissue levels of meropenem when administered by intermittent bolus versus extended or continuous infusion methods in order to recommend ways to optimize dosing regimens against resistant gram-negative infections.

A total of 50 patients were randomized to TMP/SMX plus rifampin or cloxacillin alone, and all underwent surgical debridement. After 6 patients were excluded for noncompliance, the median follow-up was 10 years. Taking into account losses to follow-up, the overall cure rate was 89.6% (43 of 48 patients), with no significant differences reported between the treatment groups. The cure rate difference between the groups was 1.6% (95% CI, -15.7% to 33.3%). In all, 5 relapses occurred (10%), and 2 of 5 patients (40%) had orthopedic implants. The findings across treatment groups did not vary after controlling for gender, age, osteomyelitis-associated comorbidities (not defined), previous osteomyelitis, fever, number of surgical debridements, closed suction irrigation, and duration of hospital stay.

This randomized, controlled study demonstrates that oral combination therapy with TMP/SMX plus rifampin is equivalent to IV therapy with cloxacillin for the treatment of MSSA osteomyelitis. In the United States, IV agents that are comparable to cloxacillin in treating MSSA are nafcillin and oxacillin (or, as oral options, amoxicillin and cephalexin). Although the study was not blinded, the criteria for failure were clearly defined. This investigation challenges the commonly accepted approach that IV therapy is the best modality for treating chronic osteomyelitis. Combination regimens of oral antibiotics offer considerable cost savings if compelling evidence of noninferiority exists. The use of orally administered antibiotics negates the need for prolonged-use indwelling IV lines, which are associated with bloodstream infections and substantial costs and are not practical in some clinical settings. Additional randomized, controlled studies are warranted to strengthen the evidence supporting the use of oral vs. IV antibiotics for the treatment of diabetic osteomyelitis.

As discussed previously in Review 1, wounds can be a highly complex microenvironment, with polymicrobial infection vs. colonization. Therefore, identification of causative organisms in osteomyelitis should be pursued aggressively beyond simple wound culture. Isolation of *S. aureus* alone is highly suggestive, but the absence of other organisms



(particularly anaerobes) may be due to culture or sampling methods. If the response to treatment of *S. aureus* is poor, expanding the therapeutic spectrum is worthy of consideration.

Finally, as an additional note, biofilm—a layer of extracellular matrix proteins with slowly replicating planktonic bacteria—has been implicated in osteomyelitis, mainly in the setting of orthopedic implants. The use of rifampin, in particular, can be helpful in targeting staphylococcal biofilms and may be a critical component of the oral combination regimen evaluated by Zimmerli and associates.¹

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SURGICAL VS. NON-SURGICAL TREATMENT OF OSTEOMYELITIS

Aragon-Sanchez FJ Cabrera-Galvan JJ, Quintana-Marrero Y, et al. Outcomes of surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement. *Diabetologia*. 2008;51(11):1962-1970.

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Senneville E, Lombart A, Beltrand E, et al. **Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study**. *Diabetes Care*. 2008;31(4):637-642.

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Aragón-Sánchez and colleagues assessed outcomes of a conservative surgical approach for the management of osteomyelitis. The authors studied 185 patients with infected and osteomyelitic diabetic foot ulcers. Patients underwent early surgical treatment within 12 hours of hospital admission. Early conservative management included debridement, minor amputations (limb salvage—e.g., phalanx, sesamoidectomy, or partial calcaneotomy, and other foot-level procedures) and major amputations (below the knee or above the knee). Infection included purulence plus ≥ 2 of the following: induration, erythema, pain, calor, lymphangitis, odor, or gas. Osteomyelitis, which was defined by probe-to-bone tests and x-rays, was confirmed via histopathology as acute, chronic, or acute-on-chronic. Primary outcomes were failure of conservative surgery because of immediate major amputation or any amputation after initial surgery. Other outcomes included 30-day mortality and healing time. Lower limb ischemia was defined as an ankle/arm index < 0.9 or transcutaneous oxygen pressure < 30 mm Hg.

The average ulcer duration was 113 days (± 264 days). Nearly half of the study population had a history of ulcer (49.7%) and more than one-third had undergone amputation (34.5%). The bone was visible in 31.3% of the patients, and probing to bone was positive in nearly all subjects (94.6% [175 of 185]). Of these, plain x-ray revealed osteomyelitis in most individuals (84.8%). Ischemia was present in 19.4% of patients, and only 1.6% (3 of 185) of patients required initial major amputation. Soft tissue infection correlated highly with any amputation ($P = .0005$). A minority of patients (17.1% [19 of 111]) ultimately required minor amputations. However, among the latter, 31.6% (6 of 19) of patients went on to undergo a major amputation.



Most patients undergoing initial minor amputations required follow-up minor amputations (93% [66 of 71]), whereas far fewer (7% [6 of 71]) went on to undergo major amputations. By study end, only a minority of patients (8.1% [15 of 185]) had undergone major amputation at any point. Subjects with acute osteomyelitis required minor amputation nearly twice as often as did those with chronic osteomyelitis (52.1% vs. 23.2%, respectively; $P = .004$). Rates of major amputation did not differ based on duration of osteomyelitis. Additionally, exposed bone occurred more frequently in patients with acute osteomyelitis than in those with chronic osteomyelitis, and probe-to-bone tests were positive more often in patients with acute osteomyelitis than those with acute-on-chronic osteomyelitis (97.8% vs 88.8%, respectively; $P < .05$).

S. aureus was the organism most frequently isolated as the cause of osteomyelitis, reported in 46.5% of cultures (95 of 176). It was present alone in 64.2% of cases with positive cultures. MRSA was less frequent (36.8% of cultures).

Amputation was more likely to occur in the presence of exposed bone, lower limb ischemia, and necrotizing soft tissue infection.

In patients without immediate major amputation, median healing time was 90 days. Wound healing following conservative debridement was 80 days (range, 12 to 365 days), vs 120 days (range, 21 to 365 days) with minor amputations. Soft tissue infection and limb ischemia were associated with prolonged wound healing.

Does early debridement of diabetic foot infections allow limb salvage and prevent the occurrence of major amputation? Because of the lack of randomization and a control arm in this study, no clear answer to this question exists. The majority of subjects with initial minor amputations required subsequent minor amputations, but the overall frequency of major amputations was low (8.1%). This may be a reflection of the degree of disease at the time of presentation, rather than an outcome related to the intervention. The low prevalence of limb ischemia (19.4%) and neuropathy (25.9%) supports this finding. High rates of *S. aureus* are not surprising and are consistent with those in the current literature. An interesting finding of the study is the more frequent bone exposure reported with acute vs. chronic osteomyelitis. This is consistent with accelerated tissue ischemia and necrosis in patients with acute osteomyelitis and the greater need for amputation in such patients compared with those with chronic osteomyelitis. Finally, prolonged healing following minor amputation or with soft tissue infection or ischemia likely reflects the severity of underlying disease at the time of presentation.

In their retrospective medical record review, Senneville and coworkers evaluated use of swab and bone-culture-guided, nonsurgical therapy on outcomes in patients with diabetic foot osteomyelitis. Nonsurgical therapy was defined as no intervention on bone during the 10 days following antibiotic initiation. Diabetic adults with suspected or confirmed osteomyelitis of a nonischemic foot were eligible to participate. Suspected osteomyelitis was defined as a foot wound lasting ≥ 2 weeks over a bony prominence, with an ulcer surface $> 2 \text{ cm}^2$ or a depth $> 3 \text{ mm}$, associated with positive probing to bone and/or radiographic findings consistent with a diagnosis of osteomyelitis. Subjects with confirmed osteomyelitis also had positive bone cultures. Bone cultures were performed in the operating room using a biopsy needle, with the incision at least 20 mm from the ulcer's edge. When bone cultures were unavailable or negative, swab cultures guided antibiotic selection. When bone biopsy results were positive, selection of antibiotic regimens was based on coverage of microorganisms isolated from bone, with no reference to swab culture results. IV antibiotics were administered for < 7 days, followed by a long course of oral antimicrobial therapy (duration not specified by the authors). The use of topical antimicrobial agents was prohibited. Remission was defined as no evidence of infection at the primary wound location or a proximal site for ≥ 12 months following treatment.

The authors evaluated 50 subjects. More than half (54% [27 of 50]) of the patients had already been followed in a diabetic foot clinic prior to enrollment, and 32% (16 of 50) of the patients had experienced a prior episode of osteomyelitis. *S. aureus* was the most common organism isolated on both swab and bone cultures, and MRSA was detected in 11.1% (4 of 22) and 10% (3 of 28) of bone and swab cultures, respectively. Gram-negative bacilli were the next most frequently isolated organisms, detected in 27.8% (10 of 22) of bone biopsy and 33.3% of swab cultures (10 of 28). Mean duration of antibiotic therapy was 11.5 ± 4.21 weeks. Treatment was guided by bone culture results in 44% (22

of 50) of patients and by swab culture results in the remaining individuals. A minority of subjects (32%) received IV therapy for the first week. The most commonly used antibiotics were fluoroquinolone/rifampin and fluoroquinolone/pristinamycin, followed by other combinations.

At follow-up, 64% (32 of 50) of subjects were in remission. Bone-culture-guided therapy was associated with higher rates of remission (81.8% [18 of 22 patients] vs. 50% [14 of 28 patients] without the use of bone-culture-based antibiotic therapy; $P = .02$). After controlling for demographic and clinical parameters, the only factor predictive of remission was bone-culture-guided therapy (adjusted OR, 4.78; 95% CI 1.0 to 22.7; $P = .04$).

A comparison of this study with the work on early conservative surgical management by Aragón-Sánchez and collaborators suggests that the patient populations were similar in both studies, with approximately half of each population having received previous care for diabetic foot wounds and approximately one-third having a history of prior osteomyelitis. Treatment failure in the studies ranged from 46% to 51%. In the study by Aragón-Sánchez and colleagues, however, subjects undergoing amputation at the initial procedure did not receive a trial of antibiotics alone. The lack of a control group in each study is problematic. Although the investigation by Senneville and associates suggests that reasonable success may be achieved with a nonsurgical approach to the treatment of osteomyelitis, the work by Aragón-Sánchez and coworkers suggests that in patients with acute osteomyelitis, a surgical approach may help prevent disease progression and the need for additional amputation. In summary, rates of success in the prevention of future amputations or local infection were similarly poor in both studies.

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MRSA OSTEOMYELITIS IS NOT ASSOCIATED WITH WORSE OUTCOMES

Aragón-Sánchez J, Lazaro-Martinez JL, Quintana-Marrero Y, et al. **Are diabetic foot ulcers complicated by MRSA osteomyelitis associated with worse prognosis? Outcomes of a surgical series.** *Diabet Med.* 2009;26(5):552-555.

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The objective of this study was to assess whether MRSA osteomyelitis is associated with worse outcomes than is MSSA osteomyelitis. The authors of the study used data from a series of 185 patients undergoing surgery for conservative management of diabetic ulcers within the first 12 hours after hospital admission. Surgical bone samples were assessed histologically and were cultured for the presence of osteomyelitis. Surgical outcomes of minor amputation, major amputation, number of surgeries, duration of hospital stay, postoperative death (within 30 days of procedure), and time to full healing were examined.

S. aureus was identified in 95 subjects (47.5% of all bone cultures) and was the only organism isolated in 64.2% of positive cultures. MRSA was present in 36.8% (35 of 95) of patients with any detectable *S. aureus*. There were no differences between the MRSA and MSSA groups in terms of prior antibiotic treatment or hospitalization. Overall, MRSA bone infections were associated with higher body temperatures (36.8° C vs. 36.5° C with MSSA; $P = .02$) and increased leukocyte counts ($P = .01$). In addition, MRSA osteomyelitis was associated with necrosis ($P < .001$) and foul odor ($P = .01$) compared with MSSA osteomyelitis. Moreover, subjects with MRSA osteomyelitis required a greater number of procedures ($P = .04$). However, there were no differences in healing times or rates of limb salvage between the groups.

MRSA diabetic infections and osteomyelitis are associated with increased acuity in clinical presentation. However, this study indicates that MRSA does not necessarily influence the outcomes of early conservative management of patients with diabetic osteomyelitis and the subsequent need for amputation. The findings of this study also

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suggest that other factors (including noncultivable anaerobes, particularly given the report of foul odor, which is considered diagnostic for anaerobic infection) may influence clinical outcomes in patients with diabetic osteomyelitis. Further investigation is warranted in order to examine these factors in greater detail.

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