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Osteomyelitis: Approach to Diagnosis and Treatment

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Summary

Osteomyelitis is a common disease with a variety of clinically and microbiologically distinct subsets. Diagnosis should begin with plain radiographs but may include a variety of imaging modalities. Cultures of the surface of ulcers or draining sinuses are often misleading, and bone cultures are necessary to determine the true pathogens of bone infections. The approach to treatment of osteomyelitis is complex, and often requires a multidisciplinary approach, with input from radiologists, vascular and orthopedic surgeons, infectious disease specialists, and wound care and rehabilitation specialists.

Introduction

Osteomyelitis has traditionally been classified into three categories.¹ The first category, hematogenous osteomyelitis, is bone infection that has been seeded through the bloodstream. The second, osteomyelitis due to spread from a contiguous focus of infection without vascular insufficiency, is seen most often after trauma or surgery, and is caused by bacteria which gain access to bone by direct inoculation (for example, a contaminated compound fracture) or extension to bone from adjacent contaminated soft tissue (for example, a prosthetic joint contaminated at the time of implantation). The third category, osteomyelitis due to contiguous infection with vascular insufficiency, is seen almost exclusively in the lower extremities, most commonly as a diabetic foot infection. Each of these three categories of osteomyelitis can present in the acute or chronic phase, in virtually any bone, caused by a variety of bacteria and occasionally fungi. Thus, the approach to osteomyelitis should be guided by several principles, but must be individualized to each unique situation.

Pathogenesis

Normal bone is highly resistant to infection. In experimental models, a large inoculum of bacteria is typically required to induce osteomyelitis.² Bacteria possess a variety of virulence factors that contribute to the development and chronicity of osteomyelitis, such as proteins called adhesins which facilitate attachment to bone³, and the ability to form biofilm, a slime layer which shields the bacteria from antimicrobial agents.⁴ In addition, the host's immune response to infection can damage bone. Several common cytokines have osteolytic properties, and phagocytes produce toxic oxygen radicals and proteolytic enzymes that can harm host cells. The inflammatory response leads to an increase in intraosseous pressure, which impairs

blood flow and leads to ischemic necrosis. This dead bone, known as a sequestrum,¹ can act as a non-living surface for biofilm attachment, allowing bacteria to adopt a lower metabolic rate and to survive in an environment with lower oxygen tension.. Poor blood flow as well as biofilm make it difficult for antimicrobial agents and host immune cells to access the bacteria.⁴

Clinical Presentation

Signs and symptoms may vary depending on the category of infection, organism, anatomic location, and host. Hematogenous osteomyelitis occurs most often in prepubertal children and usually involves the metaphysis of long bones, particularly the tibia and femur. Patients usually present with signs of acute infection such as fever, chills, pain, and local signs of inflammation.⁴ In adults, the most common site is the vertebral bodies, followed by long bones, pelvis, and clavicle. The primary blood supply of the vertebrae is the segmental arteries, which divide to perfuse segments of two adjacent vertebrae. Thus, vertebral osteomyelitis often occurs in two contiguous vertebral bodies and the intervertebral disc.⁵

In osteomyelitis due to a contiguous focus of infection without vascular insufficiency, patients often present with pain, fever, and purulent drainage from a traumatic or surgical wound. Infections involving prosthetic material may present later, and with more subtle findings.⁵

In patients who develop osteomyelitis in the setting of vascular insufficiency, infection occurs most often in the small bones of the feet. These patients may experience minimal pain because of neuropathy. Physical exam frequently reveals evidence of neuropathy and compromised vascular supply (e.g. diminished pulses, poor capillary refill). The contiguous site of infection is typically a neuropathic ulcer, though it can be a paronychia, cellulitis, or puncture wound.

Evaluation and Diagnosis

Routine exam and blood tests

The diagnosis of osteomyelitis may be difficult. If an ulcer is present on exam, osteomyelitis is present if bone is visible, or if bone is encountered when the ulcer is probed with a sterile instrument.⁵ However, the inability to probe to bone does not rule out osteomyelitis.

Routine laboratory tests are usually nonspecific. The white blood cell count is often normal even in the setting of acute osteomyelitis. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often elevated; however, they both lack specificity in the absence of other radiologic and microbiologic data. In cases of proven osteomyelitis, both tests may be used to assess response to therapy or relapse. CRP may be more reliable than ESR for assessing response to treatment in children.⁶

Microbiology

Blood cultures should always be obtained when osteomyelitis is suspected, though they are often negative except in cases of hematogenous osteomyelitis. The gold standard for the diagnosis of osteomyelitis is bone biopsy with histopathologic examination and tissue culture. When the patient is clinically stable, one should consider delaying empiric antimicrobial treatment until bone biopsy is performed. An open approach is ideal to ensure that adequate specimen is obtained, particularly when prosthetic material is involved.⁷ Needle biopsy is often used, and the sensitivity and specificity using this modality has been reported as 87% and 93%, respectively.⁸ Specimens should undergo both aerobic and anaerobic bacterial culture. In addition, fungal and mycobacterial cultures should be performed when clinical suspicion of these organisms is present.

Patients with suspected osteomyelitis often present with ulcers or draining wounds. If no purulent material is present, these should not be cultured. If bone biopsy cannot be obtained, culture of purulent material from such sites may be obtained, though it is never definitive and must be interpreted with caution. Surface cultures often grow only skin flora, and frequently miss the primary pathogen, or secondary pathogen(s) in the case of polymicrobial infection. Heavy growth of a common pathogen is suggestive but not diagnostic of its involvement. The presence of *S. aureus* in surface cultures has been correlated to its presence in deep cultures⁹⁻¹⁰.

Radiology

Several imaging modalities are useful in the evaluation of osteomyelitis (Table 1). Plain radiographs are the first step in assessment as they are inexpensive and safe, and may make the diagnosis. Bone destruction and periosteal reaction are not typically seen until infection has been present for 10-21 days.⁴ Negative films do not exclude the diagnosis of osteomyelitis, especially in acute infection.

Bone scintigraphy, also known as bone scan, is useful in the work-up of osteomyelitis. The radiopharmaceutical, often technetium-99, accumulates in areas of increased blood flow and reactive bone formation. In the setting of soft tissue infection without bone infection, the three-phase bone scan should only demonstrate uptake on the first two phases, with normal uptake on the late (3-hour) images; in cases of osteomyelitis, uptake is seen in all three phases. Specificity decreases in the setting of recent trauma or surgery, orthopedic devices, or diabetes.¹¹ Radiolabeled white blood cell scan is an alternative to bone scan, with comparable sensitivity and specificity, though it requires more technical preparation and time to perform.¹²

Computed tomography (CT) and magnetic resonance imaging (MRI) can be of great value in the diagnosis and evaluation of osteomyelitis. Both modalities show anatomic detail, including cortical destruction and soft tissue extension. CT is complicated by artifact caused by adjacent metallic implants. MRI cannot be performed in the presence of some metal implants, though some prosthetic implants are MRI-compatible.¹¹

Microbiology and Treatment

Because of the heterogeneity of disease severity, anatomic location, organism, and host, treatment of osteomyelitis is complex, and must be individualized. However, several general concepts guide therapy (Table 2).

Hematogenous osteomyelitis

Most hematogenous osteomyelitis is monomicrobial. In neonates, *S. aureus*, group B streptococci, and gram-negative enteric bacteria are the most common pathogens. In children, *S. aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* are most common.¹³ Community-acquired methicillin-resistant *S. aureus* (MRSA) is a growing cause of pediatric osteomyelitis.¹⁴ In adults, hematogenous osteomyelitis is most often caused by *S. aureus* and, particularly in the elderly, gram-negative enteric bacteria.⁴

Empiric antibiotics for acute hematogenous osteomyelitis should include an anti-staphylococcal antibiotic such as nafcillin or oxacillin, though vancomycin should be substituted when MRSA is suspected.^{13,15} Additional coverage against gram-negative enteric bacteria, for example a third-generation cephalosporin such as cefotaxime, should be added in newborns, and considered in older children. Empiric gram-negative coverage is also warranted in adults; quinolones are useful in this population.

Once culture results are available, antibiotics can be targeted more specifically to the causative pathogen.^{4,15} In children, a switch from parenteral to oral antibiotics may be warranted in selected cases, when there is a prompt response to therapy and an appropriate oral antibiotic option. Duration of therapy in children is typically 3 to 6 weeks. The risk of chronic infection increases unacceptably when effective therapy is given for less than 3 weeks.¹⁶ In adults, parenteral treatment should be given for up to 6 weeks for uncomplicated cases in which no residual nidus of infection is suspected.¹⁷

In children, acute hematogenous osteomyelitis can often be managed without surgical intervention, though the participation of surgeon in the decision-making process is advisable. In adults, however, surgical intervention is often necessary, particularly for infections of long bones. Uncomplicated cases of vertebral osteomyelitis may be cured without surgical debridement, though debridement or drainage is necessary when epidural abscess or neurologic impingement is present.¹⁸

Contiguous-focus osteomyelitis without vascular insufficiency

Osteomyelitis due to trauma with contaminated wounds is also typically polymicrobial, with *S. aureus*, gram-negative enteric bacteria, and anaerobes the most common pathogens.⁵ Osteomyelitis at the site of implanted prosthetic material may also be caused by more indolent organisms such as coagulase-negative staphylococci and *Propionibacterium*, which may present several months after prosthesis implantation.⁴

Surgical management in such cases is the cornerstone of therapy. Dead bone and foreign material must be removed, dead space must be managed with bone grafts, tissue flaps, or implanted antibiotic-impregnated material, and hardware should be removed unless absolutely necessary. When hardware is removed, antibiotic therapy should ideally be completed before new hardware is implanted. A one-stage approach with debridement alone or immediate re-implantation of hardware is less likely to achieve cure, though in specific circumstances these may be appropriate or necessary. Small studies have shown that eradication of susceptible bacteria from hardware is feasible without surgery in some situations, but further study is needed before this practice should be widely adopted.^{19,20}

Because of the high potential for treatment failure and bad outcomes, it is particularly important in contiguous-focus osteomyelitis to obtain bone and deep tissue cultures to guide therapy. If empiric therapy is necessary, it should be broad-spectrum while awaiting culture results. Specific parenteral therapy based on culture results should generally be prescribed for up to 6 weeks after the time of the last surgical intervention. When hardware is involved, rifampin may be useful as a second agent in infections caused by susceptible organisms.¹⁹

Contiguous-focus osteomyelitis with vascular insufficiency

Because osteomyelitis due to contiguous focus of infection with vascular insufficiency typically arises from a foot ulcer, it is usually polymicrobial. The most common pathogens in most case series of diabetic foot osteomyelitis are *S. aureus* (present in 31-47% of cases), streptococci (27-61%), and gram-negative enteric bacteria (20-50%). Coagulase-negative staphylococci and corynebacteria, which are rarely pathogenic in skin and soft tissue, can be pathogenic in bone in this setting, and thus their presence in a bone biopsy cannot be ignored. *Pseudomonas* species (0-15%) are occasionally seen.²¹

If empiric therapy is necessary, it should be broad-spectrum, and should include coverage for MRSA (for example, vancomycin) as well as broad gram-negative and anaerobic bacteria (for example, imipenem; piperacillin-tazobactam; a quinolone plus clindamycin; or an extended-

spectrum cephalosporin plus clindamycin). Bone biopsy should guide specific therapy whenever possible.

The role of surgery in the treatment of diabetic foot osteomyelitis is controversial. Because of heterogeneity of the disease, existing literature is difficult to interpret and generalize. Amputation, limited resection, debridement, and antibiotic therapy alone each have a place in the management of diabetic foot osteomyelitis. In cases of extensive bone involvement, deep abscess, necrosis or gangrene, amputation or limited resection is appropriate. Uncontrolled case series of antibiotic treatment for diabetic foot osteomyelitis with little or no surgical intervention have success rates of 25 to 88%.²²

The vascular supply to infected bone has a major impact on its ability to heal, and the vascular supply should be evaluated in all patients with a diabetic foot ulcer. In cases of significant limb ischemia, arterial bypass procedures significantly improve the rate of limb salvage.²³ Careful wound care, off-loading of pressure from foot wounds, and glycemic control in diabetics are all beneficial for the healing of foot osteomyelitis. The role of hyperbaric oxygen in the healing of diabetic foot osteomyelitis is unclear.²¹

Long-term antimicrobial suppression

In some situations, it may not be feasible to safely remove a piece of infected prosthetic material, or a sequestrum of necrotic bone. In such cases, it may be necessary to prescribe an oral antibiotic for long-term suppression of infection. This therapy should be based on culture and susceptibility data. It is preferable to use agents that are highly orally bioavailable, and agents that penetrate soft tissue well. For these reasons, for susceptible bacteria, quinolones, clindamycin, and rifampin are attractive choices.⁵ Because of the cumulative risks of side effects, cumulative costs, and antibiotic resistance problems, suppressive antibiotics should be avoided unless absolutely necessary.

CME Objectives and Questions

1. Readers will be able to describe the pathogenesis of osteomyelitis.
2. Readers will be able to discuss the relative merits of diagnostic imaging modalities in osteomyelitis.
3. Readers will be able to apply basic principles of management of osteomyelitis to clinical scenarios.
 - a. The most common site of hematogenous osteomyelitis in adults is:
 - a. Pelvis
 - b. Femur
 - c. Vertebra
 - d. Clavicle
 - b. Which of the following statements about diabetic foot osteomyelitis is false?
 - a. They are often polymicrobial
 - b. Revascularization is unlikely to aid healing
 - c. Broad spectrum antibiotics are often necessary
 - d. Wound care, off-loading of pressure from the infection, and tight glycemic control help the healing process

- c. Which of the following statements about diagnosis of osteomyelitis is true?
 - a. Plain films are useful in diagnosing early acute osteomyelitis
 - b. Sensitivity and specificity of MRI is superior to CT
 - c. In osteomyelitis, 3-phase bone scan should be positive only in phases 1 and 2
 - d. Ulcers with suspected osteomyelitis should not be probed

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Table 1

Imaging for Osteomyelitis

Modality	Sensitivity (%)	Specificity (%)
Plain radiographs	43-75	75-83
Computed tomography	65-75	65-75
Magnetic resonance imaging	82-100	75-96
Three-phase bone scan	73-100	73-79
White blood cell scan	80-90	80-90

Information from references ¹¹⁻¹².

Table 2
Basic principles of treatment of osteomyelitis

1	A combined medical and surgical approach is usually needed
2	Dead tissue must be removed
3	Poorly-vascularized tissue is unlikely to heal
4	Empiric therapy not guided by culture results is more likely to fail
5	With few exceptions, infection is very difficult to eradicate from prosthetic material