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Osteomyelitis

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FOCUS QUESTIONS

1. What is the pathogenesis of osteomyelitis? What is the most common bacterial cause of osteomyelitis and how may it be spread? What are the age-related differences in pathogenesis?
2. What are the early clinical findings of osteomyelitis in the neonate, in the infant, and in the young child? What are the common differences in causative organisms among these three age groups?
3. What are the laboratory tests for the diagnosis of osteomyelitis and for the assessment of effectiveness of therapy?
4. What factors are important in the appropriate use of oral antibiotic therapy in the management of osteomyelitis?
5. What are the complications of acute osteomyelitis?

Osteomyelitis, defined as an inflammation of bone generally caused by a pyogenic organism, is a common disorder of childhood. Infection most commonly is caused by blood-borne bacteria that localize in the metaphysis. Trauma or surgery also may result in direct inoculation or implantation of bacteria into the bone, or an adjacent focus of infection might extend directly to the bone, resulting in osteomyelitis.

The etiology of acute hematogenous osteomyelitis is not understood completely. Bacteremia in childhood occurs frequently, if not daily; thus, the presence of bacteria alone may not explain why infection begins. Recent trauma coincidental with a bacteremia has been postulated. The presence of an intercurrent illness (ie, chicken pox) or infection may introduce a larger number of organisms or different pathogenic bacteria into the system or alter the immune system, making the host more susceptible.

An understanding of the anatomy of bone and the pathogenesis of osteomyelitis is essential to appreciate the protean manifestations of the disorder.

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Pathogenesis

In acute hematogenous osteomyelitis, infection is localized in the metaphysis. The circulation of the bone predisposes this region to the infection. Epiphyseal and metaphyseal blood supplies generally are separate. The blood supply to the metaphysis originates when the nutrient arteries send small terminal branches that end at the growth plate. Blood flow is thought to be sluggish in this region. As the infection commences, secondary thrombosis occurs, which further creates a receptive environment for bacterial proliferation. Concomitant or preceding trauma may cause or encourage further vascular compromise to the metaphyseal microvasculature.

Metaphyseal bone is quite porous, with extensive Volkmann canals and the haversian system. Diaphyseal cortical bone is thicker and less porous. The medullary cavity of the diaphysis contains a rich reticuloendothelial system. However, in the metaphysis adjacent to the growth plate, reticuloendothelial cells are fewer, which discourages bacterial growth. The periosteum in the child is thick and is elevated easily from the bone.

Acute hematogenous osteomyelitis begins with a bacteremia, usually of unknown origin, which seeds the metaphysis. Bacterial duplication results in accumulation of inflammatory cells initially in the region of the medullary cavity and subsequently, over the next several days, to the area of bacteria in the metaphysis. The resulting inflammatory exudate builds up pressure and may begin to migrate. The pus usually does not spread down the medullary cavity because it is walled off by the inflammatory response. It tends to pass through the Volkmann canals and the haversian system of the metaphysis to the subperiosteal space. This may result in elevation of the periosteum and/or rupture into the surrounding soft tissue. As the periosteum is lifted, the blood supply to the denuded cortex and metaphysis is compromised further and the bone may become necrotic, forming a sequestrum. Reparative periosteal new bone is laid down over this area and is termed the involucrum. Because the avascular bone is relatively inaccessible to antibiotics and the immune system, this infection may lead to the development of chronic osteomyelitis.

In the neonate, the circulation of the bone is different, with nutrient blood vessels traversing the growth plate and ending in the epiphysis. Thus, infection in this age group may destroy the entire epiphysis and growth plate. These vessels generally atrophy between 8 and 18 months of age, at which time the growth plate becomes an effective barrier. Infection while these vessels are patent frequently results in a high incidence of growth disturbances and joint abnormality.

If the infection occurs in a bone that has an intraarticular metaphysis, a concomitant septic arthritis can occur as the abscess ruptures from the subperiosteal space into the joint. This occurs commonly in the hip joint, but also may occur in the shoulder, ankle, and elbow.

Acute hematogenous osteomyelitis can occur at any age, although it is most common among infants and young children. Boys are affected more often than girls. The infection can occur in any bone but has a predilection for the most rapidly growing bones, especially the long bones of the lower extremity. This may be explained in part by the higher incidence of injury to the lower extremity.

Signs and Symptoms

The signs and symptoms of acute hematogenous osteomyelitis vary and are related to the age of the patient, duration of the process, and location of the infection. Previous antibiotic treatment may alter or obscure the findings. Patients tend to present earlier in the course of the disorder due to increased awareness of the potential for osteomyelitis.

Systemic signs may be minimal in the neonate, with only irritability and poor feeding as the clue, or there may only be signs of sepsis and no

local findings. Multiple sites of infection are not uncommon in the preterm or newborn infant. "Pseudoparalysis" of a limb often is the first sign to call attention to the involved extremity, preceding soft-tissue swelling.

The most common constitutional symptoms are low-grade fever and malaise. Less often, the child presents in an acutely toxic state. A limp or failure to walk is reported in older infants and children. Pain is reported as a chief complaint in slightly more than 50% of cases. Before swelling and erythema are evident, localized tenderness over the involved metaphysis from increased pressure within the bone is the earliest finding. Joint motion also is limited because of muscle spasm, but the limitation is not as severe as in a septic joint. Sympathetic joint effusions often develop several days into the course of the illness, raising the question of a septic arthritis.

Once the infection extends through the metaphyseal cortex into the subperiosteal space, local tenderness increases and is associated with local signs of erythema, warmth, and swelling. These local findings become even more obvious if the abscess ruptures through the periosteum into the soft tissue. Pain is not as localized if the infection is in the spine or pelvis.

Diagnosis

The differential diagnosis of acute localized bone pain in a child who has systemic signs includes osteomyelitis, septic arthritis, acute rheumatoid arthritis, acute rheumatic fever, malignancy (eg, leukemia, Ewing sarcoma, and metastatic neuroblastoma), bone infarction (ie, sickle cell disease), and toxic synovitis. The cardinal rule is that any child who has fever and bone tenderness should be considered to have acute osteomyelitis until proven otherwise.

The diagnosis of acute osteomyelitis is confirmed by the presence of two of the following criteria: pus aspirated from the bone, a positive blood or bone culture, local signs of inflammation, and radiographic or bone scan changes consistent with osteomyelitis.

LABORATORY TESTS

The classic laboratory tests employed in acute hematogenous osteomyelitis are the white blood count (WBC) and erythrocyte sedimentation rate (ESR); neither is specific for infection. The WBC can vary, although frequently it is normal with a differential that is normal or shows a mild shift to the left. The ESR is a nonspecific indicator of inflammation that reflects the concentration of fibrinogen and immunoglobulin in the plasma. Usually it is elevated initially, but it may be normal and continues to increase during the first week of treatment. The ESR slowly normalizes in 3 to 4 weeks. The primary utility of the ESR is to monitor the response to treatment after the first week.

The serum C-reactive protein (CRP) concentration may be an even better laboratory test to monitor acute hematogenous osteomyelitis. It almost always is elevated at presentation and increases and decreases much faster than the ESR, reflecting the effectiveness of treatment and predicting recovery. Changes in CRP may be seen in as few as 6 hours.

The cornerstone of confirming the diagnosis of osteomyelitis is isolating the organism from the bone. Isolating an organism is of paramount importance because there is a variety of organisms that can cause acute osteomyelitis, especially in the neonate. Bone should be aspirated at the site of maximal tenderness with a 16- or 18-gauge needle in every child suspected of having acute osteomyelitis. The aspiration site almost always will be the metaphysis. The needle is advanced down to the bone and the subperiosteal space is aspirated. If no pus is obtained, the needle is advanced through the cortex into the marrow space and aspiration is performed again. The needle can be advanced quite easily because the bone is quite porous. Aspirated material is sent for Gram stain and culture. Placing the aspirate into blood culture bottles at the time of aspiration may increase the yield of organisms. Needle aspiration of bone does not cause significant changes on bone scans and, therefore, should not be postponed for that reason.

Blood cultures also should be drawn; the yield of an organism is approximately 50%. When combined with bone aspiration, retrieval of an organism approaches 80%. Previous antibiotic therapy will decrease the yield of positive blood cultures within 24 hours. However, bone should be aspirated and blood cultures drawn in spite of previous antibiotic treatment.

CONVENTIONAL RADIOGRAPHY

It may take up to 2 weeks for bony changes to appear on conventional radiographs. They are useful initially to exclude fracture or malignancy from the differential diagnosis. Conventional radiographs taken with soft-tissue technique and symmetric positioning of the limbs may reveal deep soft-tissue swelling as the lucent deep muscle plane is displaced from the adjacent metaphysis. This progresses to obliteration of the normal intermuscular fat planes as the edema spreads.

It may take up to 2 weeks for conventional radiographs to show bony changes, but bone scans can detect osteomyelitis within 24 to 48 hours.

The earliest bony changes include irregular areas of metaphyseal rarefaction that result from the absorption of trabeculae following hyperemia and necrosis. If the infection has spread through the cortex into the subperiosteal space and elevated the periosteum, periosteal new bone formation will be evident. Bony changes lag behind the pathophysiologic changes and, therefore, may appear to be progressive in spite of excellent control and eradication of the infection. Clinical examination and laboratory findings will confirm how the patient is responding to treatment.

BONE SCAN

Because the bone scan reflects physiologic alterations in the bone, it can detect acute osteomyelitis during the first 24 to 48 hours compared with

10 to 14 days via conventional radiographs. The most common agent is technetium-99m methylene diphosphonate (TcMDP), which circulates in the vascular space and is incorporated into bone following injection. Inflammation enhances vascularity and causes increased bone turnover, resulting in an accumulation of the TcMDP, which is represented as a "hot spot" on the scans compared with the surrounding tissue. These findings were used to develop the three-phase bone scan: a flow study in which images are taken at frequent intervals during the first minute postinjection; a blood pool study, taken at 5 to 10 minutes postinjection; and a delayed study taken 2 to 4 hours postinjection. In acute hematogenous osteomyelitis, all three phases of the bone scan show increased uptake.

COMPUTED TOMOGRAPHY (CT)

CT scans provide cross-sectional images of specific areas of the body. They give excellent bony detail and are especially useful in searching for extraosseous abscesses. They are most useful in the spine and pelvis (sacroiliac joint). Because of the expense, radiation dose, and frequent need to sedate or anesthetize younger patients, however, they are recommended only in select cases.

MAGNETIC RESONANCE IMAGING (MRI)

MRI does not rely on vascular changes and can define the extent and location of the inflammatory process very precisely. The inflammatory process has a low signal intensity on T_1-weighted images and a high signal intensity on T_2-weighted images.

The appropriate diagnostic procedure for osteomyelitis is aspiration of the metaphysis for culture and sensitivity.

Early in the course of the disorder, the infected area may be infarcted and, thus, avascular. Less TcMDP will accumulate in the area, resulting in a normal or cold scan. The "cold spot" has as much importance as the "hot spot."

The sensitivity of the bone scan in detecting osteomyelitis is high (90%), but the specificity is much lower. The scan indicates location of the inflammation, but it may not be able to differentiate infection from trauma or tumor. In neonates who may have multiple foci, the sensitivity in detecting osteomyelitis is only 50%.

A bone scan is not indicated in every case of osteomyelitis. It is useful if the clinical signs are poorly localized, guiding the physician to the appropriate site of aspiration and, possibly, drainage. This is particularly true in the axial skeleton (spine) and pelvis.

The gallium-67 citrate bone scan and the indium-111 oxide white blood cell scan also have been used in the diagnosis of acute osteomyelitis. However, the length of time needed for these studies, the high radiation dose, and the low yield makes them useful in only specialized circumstances.

MRI is the best imaging method for defining pus, differentiating osteomyelitis and soft-tissue abscesses, and detailing the anatomy of sequestrum and involucrum in chronic osteomyelitis. This detailed anatomic picture often is not needed in acute hematogenous osteomyelitis. Use of MRI is limited because the signal changes lack specificity for infection; they are similar to those caused by trauma or tumor. Prospective sensitivity approaches 98%; prospective specificity is 75%. Only a single area of the body can be imaged at a time, and the images are sensitive to motion by the patient, who often requires sedation or an anesthetic. It is, however, the best technique for defining chronic osteomyelitis.

Treatment

The principles of managing patients who have osteomyelitis include: identify the location, isolate the organism, select the appropriate antibiotic, deliver the antibiotic to the bacterial organisms, and prevent further tissue destruction. The highest yielding procedure to locate the site of infection and isolate the organism is culture of the metaphyseal bone aspirate.

Gram stain of the aspirate may provide the information required to select the appropriate antibiotic. If the Gram stain is negative, then selection of the antibiotic should be based on a coexisting disease, recent or concurrent infection, and age. *Salmonella* infections occur in the presence of sickle cell disease, although in some series *Staphylococcus aureus* is more common. Children who recently had chicken pox often have streptococcal osteomyelitis. *S aureus*, gram-negative rods, and anaerobic bacteria frequently are isolated from wounds; nail-penetrating injuries to the foot yield primarily *Pseudomonas aeruginosa*.

The age of the infected child often is a reliable guide to appropriate selection of the antibiotic. *S aureus* has a unique predilection for bone and is the most common organism causing acute hematogenous osteomyelitis. The organisms causing joint infection, however, vary more with age. In the neonate, both the bone and joint frequently are involved, although the bacteriology is identical whether one or both is infected. The most common organisms in the neonate include Group B streptococci, *S aureus*, and gram-negative coliforms. *Candida albicans* is a less common etiologic agent. In the older infant, *S aureus*, streptococci, and *Haemophilus influenzae* are most common. *H influenzae* needs to be considered in those up to 4 years of age, and the patient should be evaluated for a concomitant meningitis. Since the introduction of *H influenzae* type b vaccines, the incidence of invasive disease caused by this organism has declined remarkably. Children older than 4 years of age usually have *S aureus* infections. In the adolescent suspected of drug abuse, *Pseudomonas* sp and *Serratia marcescens* should be considered. Knowing the minimum inhibitory concentration of various antibiotics to the infecting organism is helpful in selecting the most sensitive antibiotic.

The route of administration of the antibiotic is not critical as long as appropriate serum concentrations are attained. The advantages of oral administration, such as the ease of administration and relatively low cost, must be balanced by adequacy of absorption from the gut and parental-

patient compliance. The following criteria often are used for the initiation of oral antibiotics: resolving clinical course (no systemic signs and diminishing local symptoms), adequate surgical debridement, attainment of appropriate serum concentration, reliable parent(s) or provider, good tolerance of the oral antibiotic, and definitive identification of the organism or response of the presumed organism to appropriate management. Oral antibiotics are not recommended to initiate treatment because of uncertain gastrointestinal absorption.

Antibiotics have been shown to enter bone and joints in concentrations that often equal serum concentrations. However, their penetration to a significant level in avascular or dead bone has not been documented. Antibiotics have been shown to enter pus and abscess cavities, but their effectiveness may be compromised in that environment (ie, by low pH).

The duration of antibiotic treatment remains in question; there are no supporting scientific studies. The wide variation in presentation, time to presentation, presence of radiographic changes, and response makes individualization necessary. In the typical course of acute hematogenous osteomyelitis that responds to treatment within 48 to 72 hours, treatment with intravenous antibiotics for 5 to 7 days followed by oral antibiotics for an additional 3 to 4 weeks usually is sufficient. However, intravenous antibiotics sometimes are used for 3 to 6 weeks. The ESR is not a useful monitor in the first week of osteomyelitis but is helpful in follow-up. Treatment often is recommended until the ESR normalizes. The CRP may aid further in determining the length of treatment. A CBC and ESR should be monitored weekly. Peak serum bactericidal titers (1:8 or greater) and trough serum bactericidal titers (1:2 or greater) also should be monitored weekly, especially if treatment is with a long-term aminoglycoside or vancomycin. Serum creatine, blood urea nitrogen, and hearing function should be monitored if therapy with an aminoglycoside is prolonged.

The role of surgery remains somewhat controversial. The literature supports all opinions, but well-controlled studies that take into account the multiplicity of variables in acute hematogenous osteomyelitis are lacking. The goal of surgery is to debride pus and nonviable tissue, to promote the action of the antibiotic, and to eliminate progressive destruction of the tissue. Surgery is indicated when pus is obtained during needle aspiration, signs and symptoms fail to improve within 48 hours, and progressive destruction is seen on radiographs (keeping in mind that radiographic changes lag behind clinical improvement). A bone specimen should be submitted to pathology for histologic assessment at the time of debridement.

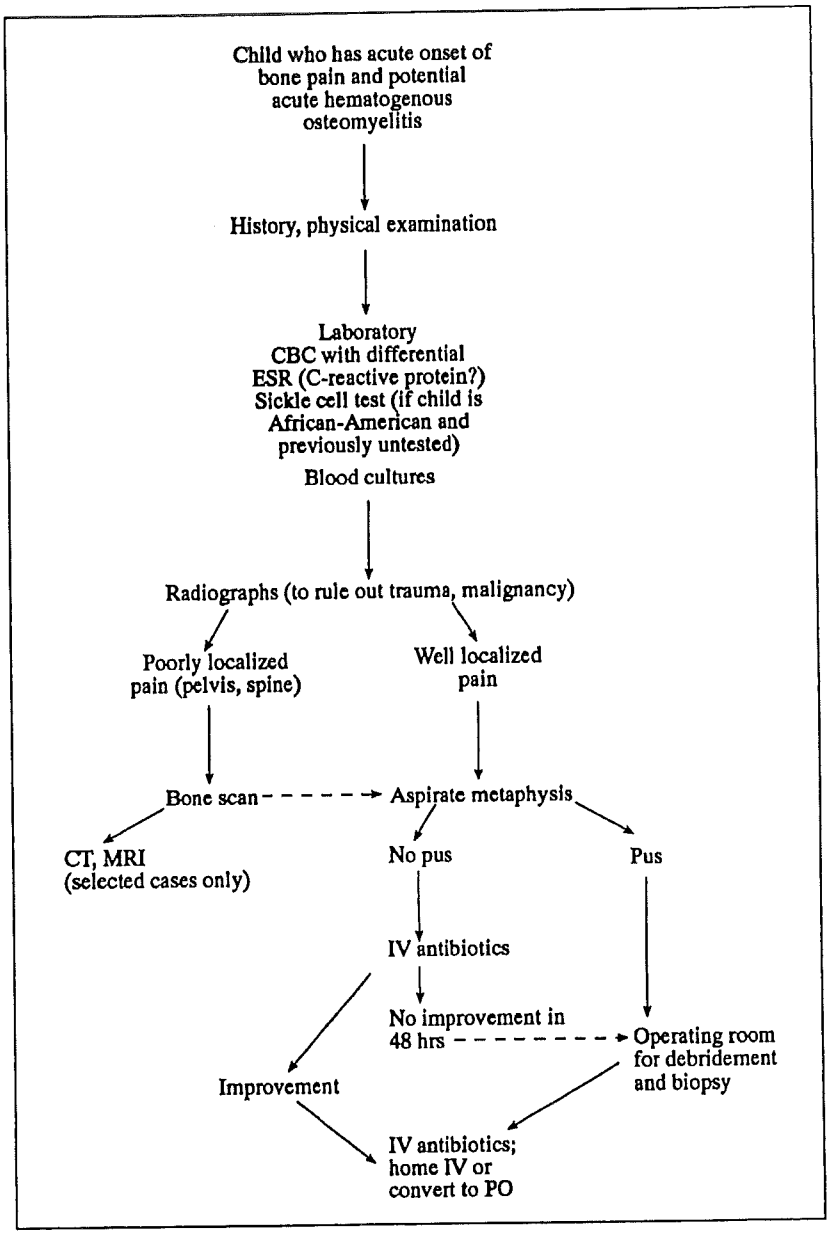

FIGURE. Algorithm for diagnosis and management of acute bone pain.

The complications of acute hematogenous osteomyelitis include overgrowth from stimulation and shortening and angulation due to growth plate damage, which is most common in the neonate. Follow-up for at least 1 year in this age group should be emphasized to the family. When a concomitant adjacent septic arthritis is present, joint stiffness, chondrolysis, and arthritis may result. Chronic osteomyelitis occurs infrequently; it usually develops in cases in which

diagnosis or treatment was delayed. The Figure outlines the approach to diagnosis and management of a child who has acute bone pain.

Special Conditions

DISKITIS

Diskitis now is recognized as a spectrum ranging from inflammation of a disk space to frank osteomyelitis of the vertebral body. It occurs primarily in children under the age of 5 years. Adolescents usually present with osteomyelitis. The pathophysiology has not been elucidated completely. The vascular supply to the disc comes from the vertebral body. As the child matures, the arterioles that ended in the disc terminate at the vertebral end plate. MRI of diskitis supports the concept that this condition is a vertebral osteomyelitis with involvement of the disc.

The diagnosis of diskitis often is delayed because its presentation can take several forms, related to age. In the younger age group, the child has difficulty in walking or standing or refuses to walk or stand. Attention is focused on the lower extremities, and the back is overlooked and not examined. Some children and adolescents present initially with back pain. A final group presents with abdominal pain. On physical examination, motion of the back often is restricted and hamstrings are tight. Frequently, gait and posture are peculiar.

The ESR invariably is elevated in diskitis. Knowing the WBC and differential is of little benefit. Blood culture is positive in fewer than 50% of cases, as is the yield from aspiration of the vertebral body or disc space. Positive cultures generally yield *S aureus*. Radiographic changes may not manifest for 3 weeks and usually are located in the lumbar spine. The initial changes are narrowing of the disc space, which progresses to end plate irregularity and, often, fusion of the adjacent vertebral bodies. Changes similar to osteomyelitis may be seen in the vertebral body. As in osteomyelitis, findings on TcMDP bone scan will predate radiographic changes.

Diskitis is an indolent and self-limiting condition. Treatment generally has consisted of bed rest, traction, pantaloon spica cast, immobilization, and antibiotics. Antistaphylococcal antibiotics should be reserved for persistent symptoms or if the child presents with systemic signs. Aspiration and biopsy is reserved for those cases not responding to antibiotics.

PUNCTURE WOUNDS

Puncture wounds of the foot are not uncommon in children, but they rarely lead to osteomyelitis. Local symptoms following the puncture wound generally resolve within 3 to 4 days. A small number of patients, however, develop increasing pain and/or signs of a cellulitis or deep infection. Culture of the early superficial infection usually yields *Staphylococcus* sp; deep infection usually is caused by *Pseudomonas* sp. It is not known if local wound care at the time of puncture will prevent osteomyelitis. *Pseudomonas* sp are cultured as part of normal skin flora and are found in the damp environment of shoes. The puncture can inoculate the bacteria into the bone directly. *Pseudomonas* sp may have a predilection for cartilage, especially the physeal plate.

Diagnosis often is delayed, and treatment generally is begun with an oral cephalosporin, which may help select *Pseudomonas* sp further. Surgical treatment is indicated in suspected cases to debride the infection and obtain adequate cultures. Two to three weeks of intravenous antibiotics usually is sufficient. Tetanus toxoid should be administered if the child has not been immunized recently.

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