Osteomyelitis: A Literature Review

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Abstract: Infection in bone and joint is still a challenging case. It gives a lot of problems and frustration to the physician and patient. The successful antibiotic therapy in most infectious diseases is abortive to achieve in bone and joint infections because the different characteristic in anatomy and physiology of these structures. Therefore, treatment strategy, including non operative and operative techniques is required to deal with such conditions. The basic principle to achieve a successful management of osteomyelitis in general is correct initial diagnosis including investigation for microbiological and pathological examinations to allow the proper and long term lasting therapy of antibiotic. For that reason, it is required to have the basic understanding in dealing with this issue, obvious and updated. It is committed to review the pathophysiology, the diagnosis, and the management of osteomyelitis in order to presents basic facilities in dealing with osteomyelitis.

Keywords: osteomyelitis diagnosis and management

Infections that occur in bone are called osteomyelitis. There are a variety of osteomyelitis based on duration, etiology, pathogenesis, extent of bone involvement, as well as age and the immune system of patient. The pathogenesis and risk factors of these conditions have been studied intensively in the past thirty years including the kinds of treatment. There are also new operative methods including the use of muscle flaps, the Ilizarov technique, and antibiotic-loaded beads for the bone infection. Despite all mentioned above, osteomyelitis cure rates are still unsatisfactory and it remains difficult to treat.1

Classification

The classification of osteomyelitis that most widely used in medical literature and in clinical practice was presented by Waldvogel et al and Cierny et al.2,3 According to the duration of the disease,
osteomyelitis is described as either acute or chronic. Other than that, according to the source of infection, osteomyelitis is classified as hematogenous if the infection originates from bacteremia and contiguous if it originates from a nearby tissue infection.\textsuperscript{45} There is also another osteomyelitis classification related to the presence of vascular insufficiency not mentioned by Waldvogel et al but quite relevant, which is the infection that occurs from direct penetration of microorganism into the bone either from an injury or surgery procedure. Tibia is the most common infected site in posttraumatic osteomyelitis and is associated with considerable morbidity.\textsuperscript{6,7}

The other classification that has commonly been used is the Cierny-Mader classification from Cierny et al.\textsuperscript{3} It includes four anatomic stages: Stage 1, medullary, osteomyelitis is confined to the medullary cavity of the bone; Stage 2, superficial, osteomyelitis involves the cortical bone only and usually originates from a direct inoculation or a contagious focus infection; Stage 3 and 4, the localized and diffuse osteomyelitis usually involves both cortical and medullary bone. Albeit, if the infectious process does not involve the bone’s entire diameter, the bone is still stable. In diffuse osteomyelitis, the entire thickness of the bone is involved that causes lost of stability. Moreover, this system classifies osteomyelitis patients as A, B, or C hosts. An A host has no systemic or local compromising factor; a B host is affected by one or more compromising factors; and a C host is severely compromised.

Etiology

A single pathogenic organism is mostly recovered from the bone in hematogenous osteomyelitis. \textit{S. aureus}, \textit{S. agalactiae}, and \textit{E. coli} are the most frequently organisms isolated from blood and bone in infants. Meanwhile, \textit{S. aureus}, \textit{S. pyogenes}, and \textit{H. influenzae} are most commonly isolated in children over the age of one year.\textsuperscript{6} Among the children after the age of four years, the incidence of \textit{H. influenzae} is decreasing due to the new vaccine for that type of bacteria.\textsuperscript{8,9} \textit{S. aureus} is the most common organism isolated in adults,\textsuperscript{5} and is the major cause of infections in both hospital patients and the community, causing diseases ranging from mild skin infections to fulminant septicemia. This organism has become increasingly resistant to methicillin.\textsuperscript{10} \textit{M. tuberculosis} causes skeletal tuberculosis as the result of hematogenous spread in primary infection. There are also some atypical mycobacteria that have been associated with osteo-articular infections. Fungal organism can also cause bone infections.\textsuperscript{11}

Epidemiology

According to a study in Glasgow, Scotland, the incidence of acute hematogenous osteomyelitis in children under the age of thirteen years has decreased from 87 to 42 per 10,000 per year over 20-year period of investigation. However, the number of osteomyelitis cases of all other sites except the long bones has remained the same while for the long bones itself the incidence rate has decreased such as the prevalence of \textit{S. aureus} that also decreased within these 20 years time period.\textsuperscript{9} Disparate from hematogenous osteomyelitis, the incidence of contagious osteomyelitis and direct inoculation of microorganism-caused-osteomyelitis are increasing that probably due to motor-vehicle accidents and the use of orthopedic fixation devices as well as total joint implants.\textsuperscript{11,12} There is a higher frequency of having contagious osteomyelitis among males and those with immunocompromised.\textsuperscript{12} Methicillin-resistant \textit{S. aureus} (MRSA) was first reported in the 1960s and rapidly spread in the 1980s. Today, MRSA is endemic in most hospitals in the world and accounts for 40-60% of all nosocomial \textit{S. aureus} infections. Community-associated MRSA (CA-MRSA) infections in both outpatients and inpatients are increasing in prevalence among adults and children.\textsuperscript{13}
Pathogenesis

Source of infection

As mentioned earlier, hematogenous spread, direct inoculation of microorganisms into the bone, and a contagious focus infection are three main causes of osteomyelitis. Hematogenous osteomyelitis usually involves the metaphysis of long bones in children and other vertebral bodies in adults. The most common causes of direct-inoculation osteomyelitis are penetrating injuries and surgical contamination. Contiguous focus osteomyelitis commonly occurs in patients with severe vascular disease.\textsuperscript{14,15}

Host factors

Host factors are primarily a defense against infections that occur in bone. However, in some conditions, host factors may predispose individuals to the development of osteomyelitis. A lack of containment of the initial infection may lead to more severe infection, e.g. three patient groups with an unusual susceptibility to acute skeletal infections are those with sickle cell anemia, chronic granulomatous disease, and diabetes mellitus.\textsuperscript{16,17} The effectiveness of the response to infection and treatment are related to many systemic factors of each responder. The systemic factors are malnutrition, renal and or hepatic failure, diabetes mellitus, chronic hypoxia, immune disease, malignancy, extremes of age, immunosuppression or immune deficiency asplenia, HIV/AIDS, as well as ethanol and/or tobacco abuse. Meanwhile, the local factors are chronic lymphedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis, small vessel disease, and neuropathy.\textsuperscript{1}

Pathology

Acute osteomyelitis

In early acute period of disease, the vascular supply to the bone is decreased due to the extending infection into the soft tissue. Large areas of dead bone may be formed when the medullary and the periosteal blood supplies are both compromised.\textsuperscript{18} However, this condition of dead bone may be prevented if it is treated aggressively and properly with antibiotics and possibly with surgery. Fibrous tissue and chronic inflammatory cells will crowd around the granulation tissue and dead bone after the infection is established. When the infection is contained, the vascular supply around the area of infection will decrease results in the ineffectiveness of the inflammatory response. Acute osteomyelitis, if ineffectively treated, can lead to chronic disease.\textsuperscript{19}

Bone tissue necrosis is an important feature of osteomyelitis. The granulation tissue developing in the infectious surface produces enzymes that resorb the dead bone. The most rapid resorption takes place at the junction of living and necrotic bone. If the area of dead bone is small, it will be entirely destroyed leaving a cavity behind. The necrotic cancellous bone in localized osteomyelitis is usually resorbed. When some of the dead bone separated from the normal bone during the process of necrosis and surrounded by a pool of infected exudate it forms a sequestrum. The action of proteolytic enzymes produced by host defense cells, mainly the macrophages or polymorphonuclear leukocytes are largely disrupted the organic elements in the dead bone. While cancellous bone is reabsorbed and may be completely sequestrated or even destroyed within two to three weeks, the separation of the necrotic cortical bone will require two weeks to six months. After that, the dead bone will slowly begin to break down and be resorbed after a complete separation.\textsuperscript{20}

Chronic osteomyelitis

The presence of necrotic bone, the formation of new bone, and the exudation of polymorphonuclear leukocytes joined with other blood components are some pathologic features of chronic osteomyelitis. The surviving fragments of periostium and endostium in the area of infection forms new bones. It forms involucrum, an encasing sheath of live bone surrounding the dead bone under peri-
osteum. The involucrum is often perforated by openings that pus may run into the surrounding soft tissues and drain to the skin surfaces results in a chronic sinus formation. It also may gradually increase its density and thickness to form part or all new diaphysis. The increasing of amount and density of the bone is according to the size of the bone and the duration and extent of the infection. The endosteum of the new bone may proliferate and obstruct the medullary canal. Especially in children, after host defense or operative removal of the sequestrum, the remaining cavity may fill with new bone. However, in adults, the cavity may persist or the space will be filled with fibrous tissue which may connect the skin surface through a sinus tract. 

Clinical Manifestations

Acute signs of infection like fever, irritability, lethargy, and local signs of inflammation may occur in children. Soft tissue enveloping the infected bone usually does not happen in children with hematogenous osteomyelitis because the effectiveness of response to infection. In general, the patient may present with pain at the involved site, swelling, erythema, and drainage. Primary or recurrent hematogenous osteomyelitis in adults usually presents vague complaints of nonspecific pain and low-grade fever, and occasionally acute clinical manifestations as those in children. 

In contagious osteomyelitis, patients may present with signs of bacteremia such as fever, chills, and night sweats especially at the acute phase. Localized bone and joint pain, and sign of inflammation around the infected area may also present in acute phase but not in chronic phase. A chronic phase can both progress either from hematogenous or contagious osteomyelitis. Local bone loss, sequestrum formation and bone sclerosis are common in chronic osteomyelitis. A localized abscess and an acute soft tissue infection may present as a sign of a sinus tract obstruction.

Laboratory Studies

Reflecting a chronic inflammation, the erythrocyte sedimentation rate is usually elevated. However, the blood leukocyte count is usually within normal range. The leukocyte count may elevate in acute case of osteomyelitis. The blood sedimentation rate usually becomes normal again after a full treatment. Therefore, the interpretation of a persistently elevated erythrocyte sedimentation rate during treatment is usually a good sign. Nonetheless, the erythrocyte sedimentation rate is not sensitive enough to diagnose acute osteomyelitis because in some people especially those with immunocompromise the erythrocyte sedimentation rate may alter for some reasons. Another inflammatory indicator that rises in both acute and chronic osteomyelitis is the C-
reactive protein CRP). It also decreases faster than the erythrocyte sedimentation rate in the three days of antibiotic treatment. The leukocyte count, erythrocyte sedimentation rate, and the CRP level should be monitored in patients at the time of admission as well as during treatment and follow up around once a week, especially in acute osteomyelitis. There is no information from the literature regarding the frequency of testing those inflammatory parameters in chronic osteomyelitis. Another laboratory tests should be performed to evaluate drug toxicity during treatment such as kidney function test (serum creatinine level and liver function test), serum albumin, and total iron binding capacity to observe nutritional status and comorbidities e.g. blood glucose level in patients with diabetes.

Microbiology
Cultures of specimens from the bone lesion as well as blood or joint fluid are performed to find out the etiology of osteomyelitis and determine the diagnosis. In stage 1 osteomyelitis (hematogenous) based on Cierny-Mader, when there is radiographic evidence of osteomyelitis, and positive result in cultures of blood or joint fluid, the need for bone biopsy may be eliminated. In other type of osteomyelitis, antibiotic treatment should be based on cultures of bone taken at time of debridement or deep bone biopsies. It is advisable to perform the cultures before the antibiotics are initiated. Empirically selected antibiotics are usually given as the first line therapy. However, before the collection of samples for cultures, the empiric antibiotic should be stopped for at least three days to avoid bias. It is not reliable to take the samples from the sinus tract, albeit, S. aureus that has grown in the sinus tract and in the bone has positive correlation.

Radiographic Findings
Lytic changes in radiographs may only appear when at least 50% to 75% of bone matrix has been destroyed. It requires careful clinical correlation to achieve clinical relevance. Increased bone marrow density in early stage of infection might be seen with computed axial tomography. In patient with hematogenous osteomyelitis, intra-medullary gas has been reported. In order to demonstrate the involvement of soft tissue infection, a computed tomography scan can also identify the bone necrotic areas. The scatter phenomenon is one disadvantage of this study, which occur when there is metal near the area of bone infection affects the scanning process results in a substantial loss of image resolution.

One useful modality that has been recognized for diagnosing the presence and extent of musculoskeletal infection is called magnetic resonance imaging. It is useful in order to distinguish either it is bone or soft-tissue infection. However, a metallic implant nearby the target area may produce focal artifacts and decreasing image quality. Radionuclide scans may be performed when the diagnosis of osteomyelitis is ambiguous. However, it is not necessary to perform the test in general.

There are no guidelines for the clinical use of radiographic imaging in diagnosing osteomyelitis. However, plain radiographs are recommended to be made because they are usually effective, economical, and simple. If the diagnosis is doubtful, it is recommended to request a magnetic resonance imaging if possible. In order to help establishing a surgical plan, a computed tomography scan can be used.

Treatment
The management of osteomyelitis includes debridement to control the infection and culture-directed antibiotic coverage. An underlying disease such as diabetes should be paid more attention too. Therefore, an attempt is made to improve the nutritional, medical, and vascular status of the patient, and also to treat the underlying diseases if possible. It requires team approach including plastic surgeons, infectious disease specialists, and other physicians.
Antibiotic Treatment

The traditional duration of treatment in any stage of osteomyelitis is four to six weeks and the revascularization of bone after debridement is approximately four weeks. However, the rational of this duration is based on the results of animal study.46 Outpatient therapy such as a peripherally inserted central catheter, a Hickman and/or a Groshong catheter has been proven to reduce treatment cost and improve patients’ quality of life.47-50 Empirical broad-spectrum antibiotics may be initiated if immediate debridement surgery have to be performed before the cultures can be obtained. Initial antibiotics therapy for long bone osteomyelitis of either nafcillin or clindamycin (or vancomycin when Enterococcus spp. are suspected) and ciprofloxacin (except in children when aminoglycoside should be used). Clindamycin, an active antibiotic against most Gram-positive bacteria, has shown an excellent bioavailability. It is currently given an initial intravenous of one to two weeks duration and continue given orally.51,52 In order to work against MRSA, linezolid has proven to be effectively working.53 The use of levofloxacin has been observed to cause decreasing in serum bacterial level below minimum inhibitory concentrations.47,54-56 Other drugs that have been proven an efficacy in the oral treatment of osteomyelitis are rifampin, cotrimoxazole, and fluoroquinolones.

Quinolones are used for Gram-negative bacterial infection in adult patients with osteomyelitis. The second-generation quinolones (ciprofloxacin and ofloxacin) have poor activity against Streptococcus species, Enterococcus species, and anaerobic bacteria.57 However, the fourth generation of quinolones such as trovafloxacin has outstanding effect of Streptococcus species and anaerobic organisms.58,59 In rare cases, trovafloxacin can lead to serious liver toxicity. None of the quinolones have reliable effect on Enterococcus species. Patients are usually on going two weeks of parenteral antibiotics before changing to a non-quinolone oral regimen. The absorption process for quinolones are excellent, therefore, it can be given orally as soon as possible to the patient. The side effect of high-dose quinolone has been reported as the damage of articular cartilage in young animals;50 therefore, the long-term use of quinolone in children and infants is concerned.

Even though in general the serum bactericidal is associated with successful outcome in treating osteomyelitis, it is not necessary to follow serum bactericidal levels because most treatment failures are due to inadequate surgical debridement rather than inadequate antibiotic efficacy.61 To be ideal, the treatment should be based on the cultures results. After that, a parenteral antimicrobial regimen is begun to cover the suspected pathogens. The treatment might me modified once the specific organism is identified. However, if the clinical presentation shows that the patient is acutely ill, the antibiotic should be given right away while waiting for the bone debridement.35

Antibiotic Treatment by Stage

Stage 1. The vascularization in children are way better than in adults and it also has an effective response to infection. Therefore, in children, osteomyelitis is usually treated with antibiotic alone.51,52 In adults, the operative intervention are often required together with antibiotics. After the last major of debridement, the patient is treated with antimicrobial therapy for four weeks. If the initial management fails and the infection is re-occurred, another four-week course of antibiotics and debridement are required. In children, oral antibiotics can also be used.1

Stage 2. Shorter courses of antibiotics are usually needed. In a study in which two-week course of antibiotics was given following debridement, the osteomyelitis was arrested in both hosts with favorable results.52

Stage 3 and 4. Antibiotics should be given for four two six weeks from the last major debridement. The failure rate is high if an adequate debridement is not per-
formed even being treated with anti-microbial agents. Even when all the necrotic tissue has been adequately debrided, the remaining bed of tissue must be considered contaminated. Therefore, the four weeks treatment of antibiotics is extremely required.¹

**Suppressive Antibiotic Therapy**

Ideally, drugs for suppression must have good bioavailability, low toxicity, and be able to penetrate bone adequately. The regimen also needs to be directed by the culture results, therefore, the causative microorganism is susceptible to the antibiotic used for suppression. Suppressive therapy using rifampicin in combination with other antibiotics has been administered during the period of six to nine months to patients with infections around implants.⁶²-⁶⁴ Suppressive therapy is traditionally administered for six months. If after discontinuation of the therapy and the infection recurs, a new lifelong suppressive regimen needs to be started.

**Operative Treatment**

The principles of treating any infections are adequate drainage, extensive debridement of all necrotic tissue, obliteration of dead spaces, adequate soft tissue coverage, and restoration of an effective blood supply.⁶²,⁶³ The operative treatment is more challenging in compromised patients for it can be life threatening. Occasionally, the procedures can lead to the loss of function, limb, or even the life of the compromised host. Therefore, standard operative treatment of osteomyelitis is not possible for all cases. Patients that considered as compromised are, in some cases, candidates for more radical treatment e.g. amputation or antibiotic suppression.¹

**Reconstruction of Bone Defects and Management of Dead Space**

Bone defect might occur following the adequate debridement, termed a dead space. The goal of dead space management is to replace dead bone and scar tissue with durable vascularized tissue.⁶²,⁶⁵ A free vascularized bone graft that usually obtained from the fibula or ilium has been used successfully to fill dead space.⁶⁶,⁶⁷ One alternative technique is to place cancellous bone grafts beneath local or transferred tissues where local augmentation is necessary. In order to temporarily maintain and sterilize a dead space, antibiotic-impregnated acrylic beads may be used. The antibiotics that are mostly used in beads including vancomycin, tobramycin, and gentamicin. In one case study of children, an additional option that may heal the soft tissue wound is the vacuum-assisted closure system. It is a device that applies localized negative pressure over the surface of wounds and aids in the removal of fluid. A study of high energy soft tissue injuries has reported that 57% of the patients did not require additional treatment or a split thickness skin graft after undergoing a split thickness pressure treatment for approximately twenty days.⁶⁸ The potential application of vacuum assisted closure system is promising. However, some studies were conducted in order to determine its efficacy and risks in patients with established osteomyelitis. One study has reported the development of an anaerobic wound infection that was possibly potentiated by topical negative pressure.⁶⁹

**Bone Stabilization**

Stabilization using plates, screws, rods and/or an external fixator must be done if skeletal instability is present at the site of infection. Internal fixation is less preferred because of its risks of secondarily infecting the sites of medullary rods and spreading the extent of the infection. Ilizarov external fixation allows reconstruction of segmental defects and difficult infected nonunions.⁷⁰ The free flaps and vascularized bone grafts techniques are also used quite often. Together, debridement and immediate muscle flap coverage are the primary surgical strategies to provide effective, single-stage treatment of chronic wounds of osteomyelitis and allow the restriction of
antibiotics to short-term use. Muscle flaps covered with skin grafts provide durable coverage while allowing subsequent ancillary procedures, such as bone grafts, to be performed.\(^7\)

**Soft Tissue Coverage**

Small soft-tissue defects may be covered with a split-thickness skin graft. In large soft-tissue defect or an inadequate soft-tissue envelope, local muscle flaps and free vascularized muscle flaps may be placed in one or two stages. Local muscle flaps and free vascularized muscle transfers improve the local biological environment by bringing in enough blood supply which is important for host defense mechanisms, antibiotic delivery, as well as osseous and soft-tissue healing. Local and micro-vascular muscle flaps as well as micro-vascular flaps alone have been used in combination with antibiotics and operative debridement.\(^7\)

Most cases of long bone osteomyelitis are posttraumatic or postoperative. Following the increasing number of accidents and orthopedic procedures performed, it is not likely that this infection rate will decrease. However, the clinician may reduce the chances that the chronic form of the infection will develop. These following procedures as surgical debridement, wound irrigation, and muscle flap or vascularized tissue grafts have major roles in dead tissue removal and treatment, eliminating bacterial load, and filling up the dead space with vascularized tissue. In order to decrease the incidence of acute and chronic osteomyelitis, early antibiotics and sensitivity-specific antibiotics also play a major role. Also, internal fixation of contaminated dead bone inevitably leads to osteomyelitis, therefore, this should be avoided.\(^7\)

**Complications**

Bone infections may develop from compromised soft tissue and bone vascularity, host compromising factors, and the virulent or resistant organisms results in further spread of infections as soft tissue inflammation, bone abscess, bone necrosis, and blood poisoning. A study has shown that in 0.2% to 1.6% of patients with chronic draining sinuses might be complicated by metaplasia of the epithelialized lining of the sinus tract, malignant transformation, and development of squamous cell carcinoma (Marjolin’s ulcer).\(^7\)

**Prognosis**

The prognosis of osteomyelitis depends on the virulence of the infecting organism, patient’s immune status, mechanism of infection, and patient’s comorbid conditions.\(^7\) Unless it is associated with sepsis or serious underlying diseases, the mortality rate has presented as low. However, the morbidity rate can appear as significant and may include localized spread to soft tissues and joints.\(^7\)

**Conclusion**

Osteomyelitis remains a challenge to treat and has significant morbidity level. The treatment goal is to prevent the spread and fix the damage. Culture-directed antibiotics therapy and complete removal of all the necrotic bone and soft tissue through operative debridement are the appropriate treatment for this condition. It is important for the patient and the caregiver to share correct understanding of the purpose of treatment including the complications that may occur during therapy or surgical interventions.

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