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(REVIEW ARTICLE)

A review on the treatment of heamotogenoues osteomylitis

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Abstract

In clinical parlance, a new infection in the bone is referred to as acute osteomyelitis. This illness is more common in youngsters and spreads through the bloodstream rather than through direct contact. When it occurs in adulthood, osteomyelitis is typically a subacute or chronic infection that develops as a consequence of an open injury to the bone and the soft tissue that surrounds it. In cases of bacterial osteomyelitis, the patient's age or a typical clinical scenario is frequently connected to the particular organism that was isolated from the disease. (i.e., trauma or recent surgery). Staphylococcus aureus has been linked to the condition in the vast majority of patients who have experienced acute hematogenous osteomyelitis. Patients who have chronic osteomyelitis frequently have bacteria such as Staphylococcus epidermidis, Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, and Escherichia coli isolated from their bodies. In order to achieve the optimum results, antibiotic treatment should begin as soon as feasible, and antimicrobial medications should be managed parenterally for a minimum of four to six weeks. Standard components of treatment include evaluation, staging, assessment of microbiological aetiology and susceptibilities, antibiotic therapy, and, if required, debridement, dead-space management, and bone stabilization.

Keywords: Osteomyelitis; Surgical Debridement; Infection; Diabetes Mellitus

1. Introduction

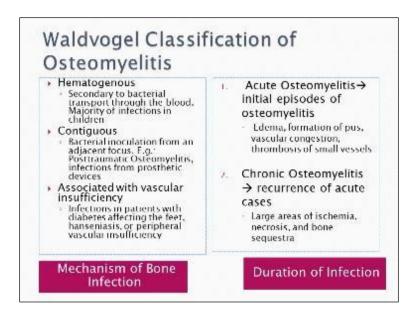
Inflammation of the bone that is brought on by a pyogenic bacterium is referred to as osteomyelitis. It has traditionally been classified as either acute, subacute, or chronic, with the presentation of each kind being determined by the point in time at which the disease first appeared. (i.e., occurrence of infection or injury). After the commencement of the disease, acute osteomyelitis can occur within one to two weeks, subacute osteomyelitis can develop within one to several months, and chronic osteomyelitis can develop after a few months.

Besides the broad types of acute, subacute, and chronic osteomyelitis, a variety of classification systems have been developed as a result of the complexity of osteomyelitis as a clinical condition. Hematogenous, contiguous, and chronic osteomyelitis are the three subtypes of osteomyelitis that are distinguished by the Waldvogel classification system[1].

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Table 1 Waldvogel Classification of Osteomyelitis



Instead of focusing on aetiology, chronicity, or other potential factors, the modern Cierny-Mader staging approach focuses on the stage of the illness process. (Table 2)[2]. The terms "acute" & "chronic" cannot be applied within the Cierny-Mader paradigm. Modifications in the patient's (or host's) health, effective antibiotic therapy, or other therapies may affect the system's phases. Other factors may also play a role in bringing about these shifts.

Table 2 Cierny-Mader Staging System

Anatomic type
Stage 1: medullary osteomyelitis
Stage 2: superficial osteomyelitis
Stage 3: localized osteomyelitis
Stage 4: diffuse osteomyelitis
Physiologic class
A host: healthyB host:
Bs: systemic compromiseBl: local compromise
Bls: local and systemic compromise
C host: treatment worse than the disease
Factors affecting immune surveillance, metabolism and local vascularity
Systemic factors (Bs): malnutrition, renal or hepatic failure, diabetes mellitus, chronic hypoxia, immune disease, extremes of age, immunosuppression orimmune deficiency
Local factors (Bl): chronic lymphedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis, small-vessel disease, neuropathy,tobacco

In spite of the fact that the classification systems for osteomyelitis that are helpful in describing the infection and determining whether or not surgery is required, the classifications do not apply to specific situations (such as infections involving prosthetic joints, implanted materials, or small bones of the body) or special forms of infection. This is because osteomyelitis can affect any bone in the body at any time.

2. Clinical Description

In children, acute hematogenous osteomyelitis typically affects the long bone metaphysis. This area is particularly prone to the problem. Patients may wait a few days to a week following the onset of symptoms before seeking medical attention. This could be a few of days up to a week. Patients exhibit symptoms of systemic sickness, such as fever, irritability, and fatigue, moreover to the local symptoms of inflammation and infection that are present in their bodies. These symptoms accompany those that have already manifested locally in their bodies. Typical clinical manifestations include pain in the area of the injured bone and limited mobility in joints adjacent to the site of injury. Acute osteomyelitis is a disease that has a variety of telltale signs and symptoms that can be seen in a patient in order to make a diagnosis.

Radiographs of people with osteomyelitis may show osteolysis, periosteal reaction, and sequestra, which are pieces of necrotic bone that are separated from living bone by granulation tissue.

Figure 1 Osteomyelitis radiograph description

Adults make up the vast majority of patients diagnosed with subacute and chronic forms of osteomyelitis. An open wound, most commonly an injury to the bone itself or to the soft tissue which surrounding it, is the most common cause of bone infections. This can be the case in the majority of cases. However, there are certain exceptions to this rule that we will discuss below. Typical symptoms include pain in the bones located in close proximity to the afflicted location, as well as redness and fluid emanating from the affected area. Subacute and long-term osteomyelitis manifest themselves in the affected area as sinus tracts that drain, deformity, instability, and symptoms of poor blood supply, flexibility in motion, and neurologic status. According to some studies, the risk of developing a serious infection in the musculoskeletal system following an open fracture might be as high as 23 percent. This finding was based on observations made by medical professionals[3]. There are several different aspects of the patient that, when combined, can result in an elevated risk of osteomyelitis. Inadequate neutrophil defense, humoral immunity, and cell-mediated immunity are some of the components involved here.

3. Diagnosis

When attempting to diagnose osteomyelitis, the most important factor to consider is the patient's clinical presentation. The information that is gained from the patient's history, physical examination, and laboratory testing are used as benchmarks for the most part when evaluating the patient's response to therapy. There is a likelihood of leukocytosis, as well as rises in both the erythrocyte sedimentation rate and the level of C-reactive protein. Additionally, there is a chance that there will be an increase in the number of white blood cells. There is a possibility that blood cultures will be positive in up to half of the children who have been diagnosed with acute osteomyelitis.

When patients with diabetes mellitus are examined, the probing of bone in the depths of infected pedal ulcers has a significant correlation with the presence of underlying osteomyelitis (sensitivity of 66 percent, specificity of 85 percent, a favorable predictive value of 89 percent, and a negative prediction of 56 percent)[4]. The diagnosis of osteomyelitis can be immediately validated through microbiological and histologic tests if the bone is palpated during the evaluation. Once the diagnosis has been confirmed, treatment can be offered. There is no requirement for any more diagnostic testing at this time.

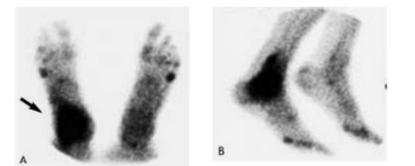
Plain film radiography and bone scintigraphy continue to be the most common tests used to diagnose for osteomyelitis of the extremities[5]. In some patients, radiographic evidence suggesting bone degeneration caused by osteomyelitis may not become visible until almost two weeks after the initial detection of the infection. (Figure 1). This is one of the possible timelines for this development. On the radiographs, there is a possibility that evidence of osteolysis, periosteal reaction, and sequestra will be visible. Sequestra are fragments of necrotic bone that are separated from living bone by

granulation tissue[6]. An infection of the bone that takes place in the subacute or chronic stage of hematogenous osteomyelitis is referred to as a Brodie's abscess. This condition can be quite painful.

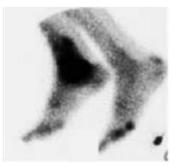


Figure 2 Plain-film radiograph of second metacarpal osteomyelitis (arrow). Periosteal elevation, cortical disturbance, and medullary involvement occur

As can be seen in Figure 2 (and also in Figure 1), the radiopharmaceutical agent of choice for nuclear imaging is technetium Tc-99m methylene diphosphonate.,See also Figure 1][7].Bone scintigraphy may not be able to check a diagnosis of osteomyelitis as the underlying medical illness in many clinical settings because of its low level of specificity[8]. Osteomyelitis can be difficult to distinguish from other conditions on a bone scan, including soft-tissue infections, neurotrophic lesions, gout, degenerative joint disease, postoperative alterations, healing fractures, noninfectious inflammatory reactions, and stress fractures. This is due to the fact that an infection of the bone marrow, as opposed to an infection of the soft tissues, is what causes osteomyelitis. In many instances, a positive result will be achieved from a bone scan even when there are no abnormalities present in the bones or joints of the patient.



Right lateral/left medial



Left lateral/right medial

Figure 3 Bone scans, anterior (A) and lateral (B), demonstrate radioactive tracer buildup at the right ankle (arrow). Osteomyelitis causes localized buildup.

When it comes to diagnosing a patient, MRI may be a beneficial method to use when the specifics are unclear. When it is suspected that a person has osteomyelitis, discitis, or septic arthritis, which is a condition involving the axial skeleton and pelvis, this imaging modality is of great assistance in the process of making a diagnosis. It is very beneficial. When it comes to making a diagnosis of osteomyelitis, MRI has sensitivity, specificity, and accuracy that are on par with or even greater than bone scintigraphy. This is because MRI uses magnetic resonance imaging technology. In addition, MRI has a advanced spatial resolution than other imaging methods, which is beneficial when evaluating the anatomical extent of an illness[6].

Ultrasonography and computed tomography scanning (Figure 3) may be beneficial diagnostic techniques during the assessment of a patient suspected of having osteomyelitis[9]. In contrast to the small regions of osteolysis in cortical bone, little foci of gas, and minute foreign bodies that may be seen by ultrasound, a CT scan can identify larger structures such as abscesses and bone surface abnormalities such as periostitis. Bone surface abnormalities (such periostitis) can also be identified with an ultrasound examination.

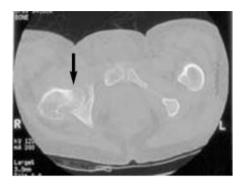


Figure 4 A CT scan showing that the right femur bone is infected. Cortical erosion, fractures, periosteal bone growth, femoral head inflammation and soft tissue swelling are all seen on the scan.

The most reliable method for diagnosing osteomyelitis is a bone exam that includes both a histopathologic and a microbiologic component. Sinus tract sample cultures are not a viable method for recognizing the organisms that are responsible for the infection. Because of this, a biopsy is strongly recommended so that the cause of osteomyelitis may be identified[10]. However, the accuracy of the biopsy is frequently hindered by factors such as inconsistent specimen collection and the usage of antibiotics in the past.

During the evaluation of a patient who may have osteomyelitis, it is important to evaluate a range of other diagnosis. Acute leukemia, cellulitis, and malignant bone tumors (such as Ewing's sarcoma and osteosarcoma) are some examples of diseases that manifest themselves in a manner that is analogous to those of other diseases.

4. Etiology

According to the information provided in Tables 3, the type of microbe (or organisms) that are isolated from individuals who have been diagnosed with bacterial osteomyelitis is frequently connected to either the age of the patient or the clinical conditions[11]. Up to 90 percent of cases of acute hematogenous osteomyelitis in otherwise healthy children are caused by Staphylococcus aureus, which has been linked in the vast majority of cases of acute hematogenous osteomyelitis in adults[12]. Patients who have prolonged osteomyelitis typically have bacteria such as the bacteria Staphylococcus epidermidis, Pseudomonas aeruginosa, S. marcescens, and E. coli retrieved from their bodies.

Table 3 Organisms Commonly Isolated in Osteomyelitis Based on Patient Age(13)

Infants (under 1 year) Group B streptococci <i>Staphylococcus aureusEscherichia coli</i>
Children (from 1 to 16 years)
S. aureus
Streptococcus pyogenesHaemophilus influenzae
Adults (above 16 years)
Staphylococcus epidermidis
S. aureus
Pseudomonas aeruginosa
Serratia marcescens
E. coli

5. Treatment

Antibiotic therapy, debridement with care of the consequent dead space, and, if essential, stabilization of bone are the components of treatment that come after the first examination, staging, and formation of microbial aetiology and susceptibilities[14]. The majority of people diagnosed with osteomyelitis benefit most from beginning antibiotic treatment as soon as possible. In order to achieve a satisfactory rate of recovery with antimicrobial treatment, treatment must be continued for at least four weeks and preferably six weeks. IV antibiotic delivery on an outpatient basis or the use of oral antibiotics are both options that might be considered in order to bring down the overall cost of treatment.

The treatment of osteomyelitis has only been the subject of a very small number of research investigations. Only five papers with a total of 154 patients suffering from this bone infection were located and reviewed[15]. Determining an appropriate course of treatment has proven challenging for a number of different reasons, including the following: debridement conceals the effect of antibiotics[16]–[18]; clinical settings and microbes are diverse; and years of follow up are required to establish that remission has been sustained. Furthermore, the majority of these trials were not conducted in a randomized fashion, did not include a control group, and only involved a limited number of patients. As a consequence of this, the majority of recommendations for the management of osteomyelitis are based not on the outcomes of randomized controlled studies but rather on the opinions of experts.

5.1. Antibiotic Therapy

The correct treatment of osteomyelitis involves the collaborative exertions of the orthopedic surgeon to collect specimens that determine the root of osteomyelitis. This is necessary in order to ensure that the patient receives the right treatment. Moreover, drainage and debridement of the acute infection must be performed whenever an abscess is present [19], and the patient's pediatrician must supervise the antibiotic treatment and evaluate the patient's clinical response.

5.2. Empirical Treatment with Broad-Spectrum Regimen

After collecting specimens, it is necessary to immediately begin empirical treatment with a broad-spectrum regimen of parenteral therapy. The agent selection for this treatment should be based on the most likely cause, which can be determined by the age of patients, clinical presentation, site of infection, and the local antibiotic susceptibility patterns. After the collection of samples, a comprehensive parenteral treatment regimen needs to be carried out as a preventative measure. There are only a select few antibacterial medications that have been granted approval by the FDA to be used in the management of osteomyelitis in babies and children. On the other hand, treatment decisions have been based on evidence-based literature, clinical experience, expert consensus, and practitioner recommendations.

Empiric therapy focused towards S aureus is the key component of antibiotic treatment, and it should make use of medications that have a high possibility of being successful. This may be determined by looking at susceptibility patterns that are reported by resident health systems or organizations. In regions of the world where the development of methicillin-resistant S. aureus as a concern has not yet taken place, the administration of semisynthetic penicillins like oxacillin or nafcillin or a first-generational cephalosporin like cefazolin is suitable. These antibiotics are called "first-generation cephalosporins." When methicillin resistance is expected due to documented susceptibility patterns, empiric therapy with clindamycin or vancomycin is acceptable; however, because of its more favoured kinetics and bone permeability, clindamycin is recommended.

The use of vancomycin as an empiric therapy is recommended if local susceptibility patterns demonstrate that a high percentage of S. aureus isolates are resistant to clindamycin. The antibiotic vancomycin belongs to the third generation of cephalosporins. In the future, it's possible that daptomycin or linezolid, two more recently developed parenteral drugs, would replace vancomycin as the gold standard.

However, at this moment, an unequivocal advice is difficult to make because there is insufficient treatment expertise dealing with paediatric osteomyelitis. Because there is a greater chance of gram-negative bacillary infection in neonatal osteomyelitis, the treatment protocol for empiric antimicrobial therapy must consist of a combination of antibiotics that cover a wider antimicrobial spectrum than those used in the treatment of osteomyelitis in children[12].

Treatment based on trial and error for osteomyelitis caused by S. Aureus It is recommended to make use of medications that are suitable for the bacterium's anticipated level of susceptibility. In addition, until the infectious agent is discovered, the usage of a cephalosporin of the third generational or an extended-spectrum penicillin with predicted action against Enterobacteriaceae and Pseudomonas, such as cefepime or piperacillin tazobactam, respectively, must be provided. When it comes to treating newborns with infections caused by gram-negative bacillary organisms, beta-lactam antibiotics are preferable over aminoglycosides. This is because beta-lactam antibiotics are more effective in treating septicemia, which frequently manifests itself clinically as neonatal osteomyelitis, and because beta-lactam antibiotics have more favorable overall pharmacokinetics when it comes to the treatment of skeletal infections.

5.3. Factors to Consider for Transitioning to Oral Therapy

Once the putative pathogen has been determined through the method of obtaining the appropriate cultures and antibacterial susceptibility is established for the isolate, it is suggested that you change to a specific antibiotic regimen and transition from IV to oral therapy [20].Clinical and laboratory parameters suggestive of a first treatment response should inform the decision to convert from iv to oral medication. In most cases, this move may be made earlier in the course of treatment without jeopardizing the patient's health or the final clinical outcome, thus it shouldn't be necessary to comply with an arbitrary defined time of parenteral medication[21].

The switch from IV therapy to oral therapy depends on a number of things, such as finding an oral agent that is efficient against the pathogen based on vulnerability assessment, the patient's improvement, which shows that the initial IV therapy was effective, a probability that the patient can take and maintain an oral agent, and when the patient will likely be discharged from the hospital. For osteomyelitis caused by Staphylococcus aureus that is sensitive to methicillin, it is best to take an oral cephalosporin like cephalexin. However, dicloxacillin should be discouraged because it tastes bad. Clindamycin is a good oral drug for treating osteomyelitis caused by S. aureus that is immune to methicillin. However, some patients have trouble taking the liquid form of the drug because it tastes bad.

Endorsement of the use of trimethoprim-sulfamethoxazole in childhood osteomyelitis is restricted due to a lack of sufficient experience with the medication. Although there is less experience with the linezolid and levofloxacin for pediatric osteomyelitis than there is with the use of beta-lactam antibacterial and clindamycin, these two medications may be the best option depending on the specifics of each patient's case. As a result, the reason for use as well as any potential side effects should be reported in a consistent and comprehensive manner.

In order to attain inhibitory concentrations at the site of infection when using orally administered beta-lactam antimicrobials, it is often necessary to deliver doses that are higher than those traditionally used (about two to four times greater). This is because bone has a reduced ability to absorb these drugs. Because of the requirement for much greater oral doses of beta-lactam antimicrobials, there has been a push for the development of approaches that can evaluate the efficiency of antimicrobials in vivo.

Typically, the achievement of oral therapy is predicted by collecting serum samples at times thought to correspond with "peak" and "trough" drug concentrations (roughly 45-60 minutes after taking the medication and within thirty minutes of the following scheduled oral dose, respectively). This is so because it is thought that this approach yields the most reliable findings.

It has been common practice to use the predicted peak serum drug concentration as the value to predict the potential effectiveness of an oral treatment, with a serum antibacterial level of at least 1:8 dilution being considered adequate. Serum bactericidal concentration at peak concentration is commonly used, but it has been shown that trough concentration, at least 1:2, can predict the efficacy of therapy and may be a better indicator of successful result [22].

Clindamycin's accumulation in phagocytes and tissues, which results in cumulative drug concentrations that are higher than those found in serum, is one of the antibiotic's many desirable properties. Because of this, the utilization of a classic standard dose treatment is probable to be helpful in the treatment of acute hematogenous osteomyelitis.

Management for S. aureus-related acute hematogenous osteomyelitis typically lasts between four and six weeks. However, current evidence indicates that oral therapy with an appropriate medicine for a period of three to four weeks is associated with successful therapy for a lot of patients if patients comply with the treatment plan. The majority of children should receive this more condensed course of antibiotic treatment if they have been diagnosed with simple acute hematogenous osteomyelitis caused by S aureus [23], [24].

Oral treatment is not acceptable when there is no available oral drug that is efficacious or when the patient is unable to tolerate an oral antibiotic.

It is possible to deliver outpatient therapy with a parenteral substance through the placement of a venous catheter as an alternative to oral medication; however, the expense of the procedure as well as the potential problems of the vascular access device are important contemplations.

5.4. Monitoring

When it comes to monitoring a patient's response to treatment, the most important thing to do is make sure they are following the treatment plan exactly as it was given and encourage them to do so. The goals of treatment are painless return of function, resolution of local and systemic symptoms, and disappearance of infection's indications. Reversal of peripheral leukocytosis and normalization of serum cytokines are secondary indicators of therapy success. In this respect, the level of C-reactive protein is crucial. Although the disappearance of abnormalities in radiography and the disappearance of postinfectious sequelae are both indicators of successful therapy, radiographic resolution cannot be used as a promptly predictor of response to therapy because it may occur after the infection has been treated successfully and clinical resolution has occurred.

6. Debridement

The procedure of surgical debridement might be difficult from a technical aspect for patients who suffer from persistent osteomyelitis[25]. The degree of success achieved by the debridement efforts is the single most essential factor in the overall success of the management efforts. After the dead space that was formed by the removal of tissue has been debrided and bone has been eliminated, it is necessary to fill in the vacuum that has been left. This can only be done after bone has been removed. During the process of dead space management, methods such as local myoblast, free tissue transfers, and the usage of antibiotic-infused beads are utilized. In order to improve both the circulation of blood in the area and the delivery of antibiotics, techniques that specifically target soft tissue have been devised.

7. Special Cases

7.1. Vertebral osteomyelitis

The most prevalent cause of vertebral osteomyelitis is an infection that began in the disc space and spread throughout the body as a result of surgery or hematogenous dissemination. Other potential causes include trauma, the spread of infection from neighboring tissues, and postoperative problems after spine and disc surgery. Patient risk factors for this condition include the presence of an extraspinal infection site, urinary tract instrumentation, internal vascular catheter, hemodialysis, IV drug use, malignancy, and diabetes mellitus [26]. In most cases, vertebral osteomyelitis is accompanied by excruciating pain as well as a diminished capacity for function.

When it comes to diagnosing pyogenic vertebral osteomyelitis, (MRI) is a crucial imaging modality[13]. Even though there may be substantial bone involvement, this type of osteomyelitis can typically be treated without the need for surgical intervention. Antibiotic treatment that lasts for a full six weeks is the standard recommendation.

7.2. Prosthetic Joint Infection

Infections of prosthetic joints are almost often caused by staphylococci that are negative for the coagulase enzyme. The most effective treatment involves the removal of the prosthesis surgically, as well as the administration of antibiotics intravenously. The joint is removed and another joint is implanted after the patient has undergone an intravenous treatment regimen lasting anywhere from two to six weeks[27]. The utilization of antibiotic-infused beads and antibiotic-loaded prostheses are both examples of potential treatments for infections that might occur in prosthetic joints.

7.3. Diabetes Mellitus

In patients who also have neurologic or vascular problems, diabetes is a substantial contributing factor in osteomyelitis. This is especially true when patients have both conditions[27]. These infections typically result in the isolation of a variety of organisms, such as P. aeruginosa, staphylococci, and anaerobes. It is possible that an initial hospitalization will be required in order to evaluate the patient's vascular supply, determine the bacteria that are responsible for the infection, remove any dead tissue, drain wounds, and ensure patient acquiescence.

8. The follow up

Patients diagnosed with osteomyelitis benefit most from beginning antibiotic treatment as soon as possible, before the condition has caused substantial bone loss. While receiving therapy, patients should be closely observed for any worsening of their condition. Following the end of treatment, the patient's response to the treatment as well as their overall health should be taken into consideration when planning follow-up care.

9. Summary

Acute hematogenous osteomyelitis often starts in the metaphysis of a long bone, but it can spread to the periosteum and other structures if treatment is delayed. S aureus is the most prevalent infectious agent in pediatric instances, although S agalactiae and Enterobacteriaceae are also possible in newborn cases. Clinical manifestations of osteomyelitis include fever, mild peripheral leukocytosis, and raised serum acute inflammatory phase reactants such C-reactive protein, as well as localized discomfort at the site of infection and impaired function of the afflicted limb or structure. The diagnosis of osteomyelitis can be aided by imaging investigations, specifically triphasic 99mtechnetium scanning and magnetic resonance imaging (MRI), particularly in the early stages of the disease. Pathogen identification using in vitro susceptibility evaluation and an antibiotic regimen that may administer therapeutic doses to the site of infection form the basis of effective anti-infective therapy. The efficacy of anti-infective medication given orally may be predicted by measuring serum bactericidal concentrations, hence it is reasonable to switch from parenteral to oral administration when clinically feasible. Until local and systemic inflammatory symptoms subside, painless function of the affected area is restored, and serum markers of acute inflammation, especially C-reactive protein, have returned to normal, antimicrobial therapy for acute hematogenous osteomyelitis should continue for 3 to 4 weeks.

10. Conclusion

Acute hematogenous osteomyelitis, in conclusion, is a life-threatening illness that calls for speedy diagnosis and treatment to avoid complications. If not treated immediately, the infection can spread from the metaphysis of a long bone to the surrounding joints and subperiosteal areas. Acute inflammatory phase reactants in the serum are high, and there is localized discomfort and decreased function of the afflicted limb or tissue. Pathogen recovery through aspiration of metaphyseal or subperiosteal infection or organism recovery via blood cultures confirms the diagnosis. The diagnosis of osteomyelitis can be aided by imaging investigations, especially triphasic 99mtechnetium scanning and magnetic resonance imaging. Recovery and identification of the causative organism in an infection are crucial steps in planning anti-infective therapy, and antibiotic regimens must be designed to provide therapeutic concentrations to the site of infection. Antimicrobial therapy generally lasts between 3 and 4 weeks and must be maintained until symptoms subside and serum indicators of acute inflammation return to normal. Successful results and the avoidance of long-term consequences can be achieved when osteomyelitis is diagnosed and treated promptly.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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