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Review of contemporary knowledge of Osteomyelitis diagnosis

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ABSTRACT

Osteomyelitis is an inflammation of the bone caused by a pyogenic organism that affects about 13 and 90 out of every 10 000 children and adults respectively. Symptoms of osteomyelitis are often nonspecific, including fever, chills, fatigue, lethargy or irritability. The major cause of bone infections is Staphylococcus aureus, however other pathogens may also lead to osteomyelitis. Due to nonspecific clinical picture and pathogenesis of osteomyelitis, the diagnostic process may be difficult, especially in the chronic form of the disease. It is essential to recognize this interdisciplinary malady and carry out a diagnostic process of osteomyelitis. The physical examination is extremely important in recognizing the osteomyelitis. The doctor ought to note scars, wound, erythema or oedema over the involved area and ask for systemic symptoms and bone pain. Subsequently, a physician should commission laboratory tests and microbiological examination, in order to verify the pathogenic organism, which must be treated with antibiotics. To put the right diagnosis, other studies such as plain radiography, magnetic resonance imaging, computed tomography, nuclear modalities must be performed. In differential diagnosis, other diseases such as bone tumours, fractures, Charcot Arthropathy, soft tissue infection, gout, osteonecrosis, and SAPHO syndrome must be considered. When both the diagnosis and the differential diagnosis is done, antimicrobial therapy is a treatment of choice together with an eventual surgical treatment which may be essential in certain cases. The differential diagnosis in patients with bone pain and systemic symptoms may be sometimes misleading and complicated. It is important, both for physician and patient, to recognize, carry out diagnostic and

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differential process in a way that a proper treatment shall be applied as soon as possible in order to avoid its complications, including even in an amputation of the affected limb.

***Keywords*:** osteomyelitis, inflammation, pet, ct, mri, scintigraphy

1. INTRODUCTION

Osteomyelitis is an inflammation of the bone caused by a pyogenic organism that affects about 13 out of every 100 000 children and approximately 90 per 100 000 adults [1,2] The major cause of bone infections is Staphylococcus aureus, which leads to acute hematogenous osteomyelitis. *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa, Serratia marcescens* and *Escherichia coli* are commonly isolated in patients with chronic osteomyelitis [3] (Table 1). Osteomyelitis can affect both children and adults. [3] Acute osteomyelitis occurs predominantly in children and affects the adjacent ends of long bones, while chronic osteomyelitis is more common in adults and mostly affects the vertebrae and the pelvis [4]. Acute osteomyelitis can usually be cured with antimicrobial therapy alone. [5] In contrast, treatment of chronic osteomyelitis with antibiotic therapy alone is rarely successful. In the setting of chronic osteomyelitis, an adequate surgical debridement of the affected bony tissue accompanied with antimicrobial therapy is essential [6].

2. CLASSIFICATION

Throughout the history, osteomyelitis has been categorized in various classification systems, including those based on the onset of the disease, but recently only two are in use - those described by Lew and Waldvogel and another by Cierny and Mader (Table 1), out of which the latter is preferred. [3,7,8]

Lew and Waldvogel's osteomyelitis is based on the onset of the disease (acute/chronic) and the mechanism of infection (hematogenous or secondary to a contiguous focus of infection). Chronic osteomyelitis may be further subdivided regarding the presence of vascular insufficiency. This classification is purely etiological and does not involve any specific therapy. [3,7,8]

Cierny and Mader classification, on the other hand, emphasizes the site of an affected portion of the bone, the physiologic status of the host as well as the local habitat. This scheme implicates the treatment and prognosis of osteomyelitis: stage 1 (medullary osteomyelitis) can usually be treated with antibiotics alone, otherwise stages 2, 3, and 4 (superficial, localized, and diffuse osteomyelitis) which usually require aggressive debridement, antimicrobial therapy and subsequent orthopaedic reconstruction [8-10].

3. PATHOPHYSIOLOGY

Osteomyelitis can arise as a result of hematogenous seeding, adjoining spread of infection to the bone from adjacent soft tissues and joints. This kind of inflammation disease may also ba consequence of direct inoculation of infection into the bone as a result of trauma

or surgery. Osteomyelitis seeded hematogenously is usually monomicrobial, while osteomyelitis due to contiguous spread or direct sowing is most commonly polymicrobial. [5]

Metaphysis is by far the most common site of infection in the setting of long-bone hematogenous osteomyelitis. [11] Generally, blood vessels nourish the bones through penetrating the midshaft of the bone and afterwards travelling toward both ends. However, patients who suffer from osteomyelitis is characterized by decreased blood flow in bone's blood vessels. [8]

The inflammatory process in osteomyelitis leads to increased intramedullary pressure, subsequently to rupture the bone cortex through the periosteum. Moreover, it interrupts the periosteal blood supply, leading to necrosis. The radiographic examination can visualize pieces of separated bone (known as sequestra). In the areas of periosteal damage formats new bone which is called involucrum. In some cases, a sequestrum can evolve into an involucrum as it is encased with new bone growth. [8,12]

Acute osteomyelitis is an infection in the bone prior to the development of sequestra. The development of sequestra may be relatively slow (such as in vertebral osteomyelitis) or relatively rapidly (such as osteomyelitis in the setting of prosthetic devices or compound fractures). Following formation of sequestra, the infection is considered chronic osteomyelitis. Other signs of chronic osteomyelitis include the formation of an involucrum, local bone decline, and sinus tracts (whether the extension of infection through cortical bone is present). [8,12]

In the setting of vertebral osteomyelitis, two endplates of the neighbouring vertebra are frequently involved in the infection. This observation can be justified by the blood supply anatomy: one arterial vessel splits to supply the neighbouring endplates of two vertebrae. [8]

4. CLINICAL FEATURES

Acute osteomyelitis, predominantly occurring in children, features the metaphysis as the most common site of an infection. In the clinical picture, these patients usually present with both local signs of inflammation as well as systemic signs (i.e. fever, irritability and lethargy). Local signs of inflammation feature tenderness over the site of infected bone which is accompanied by a restricted range of motion of adjacent joints. [3]

Subacute and chronic type of osteomyelitis, on the other hand, is more common in adults and usually secondary to the bone and surrounding soft tissue open wound injury. Clinically the affected site present with localized bone pain, erythema and drainage of the surrounding area as well as instability and deformity accompanied by impaired vascular circulation. [3]

It is important to notice, that diabetic patients are a high-risk group for developing chronic osteomyelitis, which may present atypically in its physical findings. Patients with diabetic foot, especially with cutaneous ulcers with a diameter larger than 2 cm^2 and simultaneous bone exposure are most likely to develop chronic myelitis. [13,14] In case of suspected cases, a probing to bone test may be performed in order to diagnose osteomyelitis in the affected site. The tests efficacy of DM pedal ulcers sensitivity and specificity equals 66% and 85% respectively. It is considered to be one of the best initial diagnostic tests in the setting of emergency departments as positive results highly suggest osteomyelitis. [15]

5. LABORATORY TESTING

Laboratory findings are usually nonspecific. Erythrocyte sedimentation rate and C-reactive protein may be normal or slightly elevated in cases of chronic osteomyelitis. Patients with acute osteomyelitis may present with leukocytosis. A blood culture may be positive in approx. 50% of the cases of acute osteomyelitis, but it has been noted that test's sensitivity increases in the setting of vertebral disease and hematogenous infection respectively. [16,17]

6. DIAGNOSIS

Diagnosis of osteomyelitis usually is based on correlation of the clinical picture with bacteria culture from a bone biopsy. Patients that show clinical features of osteomyelitis for at least two weeks initial evaluation of suspected osteomyelitis involves plain X-Ray of the involved area. In cases of symptoms that last less than 2 weeks other more sensitive imaging studies should be used. MRI is considered to be the most sensitive imaging modality available today. If MRI is unavailable, CT study is a good alternative test. In cases when MRI and CT are precluded by the presence of metal in the affected area (for instance orthopaedic prostheses), nuclear studies are recommended. In general, the diagnostic algorithm should be based on country-approved guidelines with considerations of available imaging methods [18,19].

6. 1. Plain Radiograph (X-Ray) is considered as the most reasonable initial imaging test as its relatively the most cost-effective study with the sensitivity ranging from 43 to 75% and specificity of 75% - 83%, especially after the 2-week onset of the disease. Its major limitation is low sensitivity in cases of early osteomyelitis as well as inability to distinguish it from fracture or Charcot arthropathy. Radiographic findings may include focal osteopenia, cortical loss, bony destruction reactive sclerosis sequestra and involucrum. Osteomyelitis in the setting of orthopaedic prostheses may show periprosthetic lucency as well as fracture nonunion. [3]

6. 2. Magnetic Resonance Imaging (MRI) – a method of choice in imaging of acute osteomyelitis with sensitivity 90-95% and specificity 80-95%. This method is useful especially in evaluating the extent of cortical destruction as well as soft tissue and bone marrow inflammation. Although i.v. contrast is not essential for detection of osteomyelitis, it may provide better distinction between necrotic tissue and abscesses. Due to its high predictive value (negative predictive value of 98% and positive predictive value of 79%), a negative MRI scan result usually is sufficient to exclude osteomyelitis in cases when clinical symptoms are absent for more than 1 week. In case of suspicion of early vertebral osteomyelitis, it is essential to note that it can mimic degenerative changes, thus if MRI is negative for infection despite persisting clinical suspicion of an infection, it is recommended to repeat MRI test after 1-2 weeks and/or supplement it with nuclear studies (preferably 18F-FDG PET-CT) [12,20].

6. 3. Computed Tomography (CT) - features higher sensitivity in comparison to plain radiography. It allows better assessment of cortical and trabecular integrity as well as

evaluation for the presence of osseous sequestra and involucrum. Other findings may include blurring of fat planes, increased density of fatty marrow, periosteal reaction. In the setting of chronic osteomyelitis, this test features sensitivity of 67% and specificity of 50%. [21] Disadvantages of this modality include patient exposure to radiation as well as considerable costs and limited availability (the latter two similarly to the MRI scan).

6. 4. Nuclear Imaging – preferable imaging techniques in setting when MRI or CT scans are precluded. Nuclear imaging features very high sensitivity for inflammation detection, especially reliable in the evaluation of acute osteomyelitis, but it is essential to note that specificity in osteomyelitis diagnosis varies between the studies offered. Major limitations include limited ability of differentiation between recent trauma, septic arthritis, degenerative joint disease, bone tumours and Paget disease, although 18F-FDG PET-CT shows promising results and it may overcome the limitations of other well established nuclear imaging modalities. [22,23]. Recent methods used in the diagnosis of osteomyelitis include 18F-FDG PET-CT, three-phase bone scan and tagged white blood cell scans.

6. 4. 1. Positron Emission Tomography - Fluorine-18-fluorodeoxyglucose positron emission tomography (18F-FDG PET-CT) is based on a use of glucose analogue that accumulates in leukocytes, which subsequently accumulates at the site of infection. This study is featured with a specificity of 75% - 99% and sensitivity of 91% - 99% and can be used for diagnosis of both acute and chronic osteomyelitis. Recent studies also suggested that this method may be useful in differentiation between Charcot arthropathy and osteomyelitis, making it excellent if other imaging studies show to be inconsistent. Although it may seem to be promising study, it has several disadvantages, such as the inability to differentiate infection from a tumour, high costs and very limited availability [24,25].

6. 4. 2. Three-phase bone scan - uses a radionuclear tracer (most commonly technetium-99m bound to phosphorus-containing compound) that accumulates at the sites of bone turnover and sites of increased osteoblast activity thus making it a very sensitive (sensitivity up 85-95%) for presence of osteomyelitis but since similar processes can be observed in other settings, its specificity is considerably low (ranges between 25% - 28%). This method involves several gamma camera scans of the affected area following the tracer injection: blood flow phase (immediately after injection), blood pool phase (approx. 15 min after injection) and osseous phase (up to 3-4 hours after injection). In patients with both acute and chronic osteomyelitis, all three phases show an increased uptake of the tracer at the affected site. This study enhanced with Single photon emission computed tomography (SPECT-CT) has shown to noticeably increase the accuracy of the three-phase bone scan, allowing better distinction between osteomyelitis and soft tissue infection as well as improved localization of osteomyelitis. [19,26] It is important to note that SPECT-CT study uses a low-dose CT (four-fold lower radiation dose than conventional CT) and does not involve the use of i.v. CT contrast making it a safer alternative to CT scan alone but subsequently comes with limited diagnostic value in comparison to conventional CT quality. [27]

6. 4. 3. Tagged white blood cell scan - nowadays most commonly - uses technetium-99m labelled white blood cells (WBCs). During this study, patient's blood is drawn and WBC is separated for labelling. After a few hours labelled WBCs are returned to the patient's

circulation system via i.v. injection. The scan is taken in up to 24 hours after the injection. The principle of this study is based on the accumulation of tracer-labelled WBC accumulation at the site of inflammation or infection. Depending on the tagging agents used, compound stability, as well as the resolution of the scan, differs, thus it is recommended to discuss the scan option with a nuclear physician in advance. This study features similar sensitivity to the bone scan (ranging from 72% - 100%) but specificity can be lowered if x-ray show to be abnormal (67% - 100%). It is important to notice that it's sensitivity and specificity gradually decreases with time, thus it is good for detection of acute osteomyelitis with a considerably worse detection rate of chronic osteomyelitis (in such cases other nuclear studies are recommended, for example, 18F-FDG PET-CT or three-phase bone scan). Similarly to the three-bone scan, this study can be SPECT-CT enhanced with all of the benefits mentioned above). [28,29]

6. 5. Ultrasonography (US) should be considered a useful diagnostic tool if other imaging modalities are not readily available. Although the US is not good for bone imaging, it may depict superficial changes to the cortical bone. In the setting of osteomyelitis, an elevation or pus-based thickening of the periosteum may be observed. Another advantage of this test involves the ability of US-guided aspiration of fluid collections and/or abscesses as well as it can be used in guidance in needle biopsies. [30-32]

7. DIFFERENTIAL DIAGNOSIS

7. 1. Charcot Arthropathy – belongs to one of the most challenging in differential diagnosis with osteomyelitis since it shares similar clinical features. In addition, Charcot arthropathy commonly develops skin ulcerations which in turn may result in secondary osteomyelitis. Imaging studies may be inconsistent in differential considerations, but contrast-enhanced MRI may give a hint if the study shows fluid collection, significant marrow abnormalities and/or replacement of soft tissue fat. [33]

7. 2. Bone tumours – especially in pediatric patients; those most common in considerations include Ewing sarcoma, osteosarcoma, neuroblastoma and metastase**s.** Usually differentiated by X-Ray study followed by a bone biopsy [34].

7. 3. Fractures/trauma – recent or old poorly managed fracture may show similar features to osteomyelitis in the radiographic study and if the imaging studies are inconsistent, especially in the setting of the absent or poorly ongoing healing process, a bone biopsy may play a major role in differential diagnosis.

7. 4. Soft tissue infection – it is essential to note that soft tissue infection may occur alone or concomitantly with osteomyelitis. Usually, probing to bone study is sufficient for the diagnosis of osteomyelitis. In setting that chronic soft tissue infection fails to improve despite applied antibiotic therapy, osteomyelitis may be suspected. In this case, imaging studies may help to determine whether there is involvement of bone (especially seen in diabetic patients). [35]

7. 5. SAPHO syndrome – Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome includes neutrophilic dermatoses that are associated with aseptic osteoarticular lesions and diagnosis can be usually based on symptoms. In cases when clinical picture lacks characteristic pustulosis and synovitis, SAPHO may mimic osteomyelitis and its diagnosis should be always based on correlation with laboratory tests results along with imaging studies. [36]

7. 6. Osteonecrosis – avascular necrosis of bone can be usually suspected in settings of steroid, radiation and/or bisphosphonates use and in such cases, it is usually sufficient in differentiation from osteomyelitis. [37]

8. TREATMENT

Treatment of osteomyelitis generally involves antibiotic therapy accompanied by pain medications. In some cases, osteomyelitis may require surgical debridement of the necrotic tissue. Surgical treatment may also be required in the setting of prosthetic hardware placement, especially in the setting of prosthesis-associated osteomyelitis. Antibiotic treatment should be based on the identification of pathogens from bone cultures obtained at the time of bone biopsy or surgical debridement. It is preferable to avoid antibiotic therapy in cases of stable patients until tissue cultures can be obtained. In cases of unstable patients or circumstances that culture results are not obtainable, broad-spectrum empiric therapy should be administered. Treatment for acute osteomyelitis is usually 4-8 weeks long and consist of pathogen-directed therapy [34].

9. CONCLUSIONS

Monitoring of treatment progress in correlation with a clinical picture of the patient is essential to determine whether the given course is the best for the patient or requires any adjustments. In cases of favourable response to the ongoing therapy follow-up imaging studies are not recommended. A suspicion of therapy failure should be raised in cases when the patient has a non-degrading persistent pain and/or markedly persisting elevated markers of systemic inflammation. In this setting, a follow-up laboratory tests and imaging studies are recommended, especially in the evaluation of the evolutionary changes in paraspinal and epidural soft tissues changes. If the evidence of therapy failure is present, a consultation with a neurosurgeon and infectious disease physician may be necessary [6].

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Table 1. Classification systems of Osteomyelitis.

Waldvogel Classification System for Osteomyelitis	*Cierny-Mader Staging System for Osteomyelitis Anatomic type*
- Hematogenous osteomyelitis - Osteomyelitis secondary to contiguous focus on infection - No generalized vascular disease - Generalized vascular disease - Chronic osteomyelitis (necrotic bone)	Stage 1: medullary osteomyelitis Stage 2: superficial osteomyelitis Stage 3: localized osteomyelitis Stage 4: diffuse osteomyelitis *Physiologic class* A host: healthy B host: Bs: systemic compromise Bl: 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 or immune deficiency Local factors (Bl): chronic lymphoedema, venous stasis, major vessel compromise, arteritis, extensive scarring, radiation fibrosis, small-vessel disease, neuropathy, tobacco abuse

Table 2. Most common etiological microorganisms in relation to age group.

Organisms Commonly Isolated in Osteomyelitis Based on Patient Age		
Infants (< 1 year)	Children (1 to 16 years)	Adults (> 16 years)
Group B streptococci *Staphylococcus aureus* *Escherichia coli*	*S. aureus* *Streptococcus pyogenes* *Haemophilus influenzae*	*Staphylococcus epidermidis* *S. aureus* *Pseudomonas aeruginosa* *Serratia marcescens* *E. coli*