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OSTEOMYELITIS OF MAXILLA IN COVID-19 ERA—ACTUALITY OR THE UNFORESEEN: A SYSTEMIC REVIEW

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Abstract

Osteomyelitis of maxilla in Covid-19 patients who were diabetic and was on high dose of steroid, recovered from the disease but had extensive osteomyelitis of maxilla later .its clinical presentation was slightly different from regular osteomyelitis like multiple draining sinuses intraorally, can be misdiagnosed as simple gingival abscess. So early diagnosis and proper management with surgical procedures and antifungal drugs can prevent functional and esthetic problems.

Key Word- Osteomyelitis, Maxilla, Covid-19, Gingival abscess, Diabetic.

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INTRODUCTION

Osteomyelitis is an inflammatory bone disease affecting bone marrow. It often compromises of cortical bone and periosteum. One of the 1st reports on osteomyelitis was published in 1832 by British physician Sir Benjamin Brodie, who described a type of abscess, which in earlier days was known as the Brodie abscess, and which showed one of the chronic features of osteomyelitis [1]. Inflammation originates in the bone marrow, and reaches cancellous bone. It then passes through blood vessels, fibro-elastic tissues, and ultimately to the periosteum, compromising the vascularity of bone tissue is compromised leading to bone necrosis and sequestration.

Osteomyelitis is generally found in middle aged to older patients.

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In head and neck, the mandible is more often affected than maxilla. This is because in maxilla, there is cancellous bone tissue with rich vascular supply. This rich blood supply hampers bacterial colonization as cellular response is improved which thus counteracts bone invasion. nevertheless, in the upper jaw anterior region, blood supply is juxta-terminal which favours bone sequestration which can result in oral-nasal communication [2,3].

Maxillary osteomyelitis is more commonly seen in infants or children as compared to adults because maxilla includes dental buds and so, there is a more intense vascular irrigation, which can become the origin of hematogenous osteomyelitis or by a neighbouring skin process due to a staphylococci infection in the infant [4].

Mandibular blood supply is very singular: when there is a concentrated osteomyelitic infection, there are more chances of formation of bone sequestrations. This is due to presence of a terminal type irrigation which cannot reimburse peripheral blood supply of gingiva and periodontal tissues. Due to vascular thromboses and endoarteritis or sympathetic and parasympathetic reflexes, vasoconstriction occurs therefore, osteomyelitis can be found in either of the two jaws [5].

Osteomyelitis of the jaws remains a dreadfully distinctive condition of the facial skeleton that represents a challenge for the medical practitioner as well as the patient, despite all recent advances in diagnosis and advanced treatment modalities. Within the past decades the clinical appearance of osteomyelitis cases has modified dramatically. Frequently osteomyelitis is associated with a pre-existing infectious disease which often requires multiple surgical interventions resulting in facial disfigurement and scarring.

Since the half of the 20th century, there has been a dramatic reduction within the incidence of osteitis cases involving the jaws [6] due to the introduction of antibiotics alternative factors like improved nutrition and higher convenience of medical and nursing facilities, particularly together with advances in preventive medicine and oral hygiene. Early diagnosis is also now possible with the aid of various diagnostic imaging modalities which ultimately improved the morbidity related to this disease [6, 7].

During Covid era there was drastic increase in opportunistic infections due to decreased immunity, mishandlings of medications used for treatment and

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improper/delayed diagnosis. One such example is increase in fungal infections/diseases. The involvement of fungus in the bone marrow renders the fungal organisms' growth, affecting the endothelial lining of vessels causing vascular insufficiency eventually leading to necrosis of the bone developing into fungal osteomyelitis. Fungal osteomyelitis offers high diagnostic difficulty and is more aggressive.

The current global health issue, coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2) and has become an emergency per se. COVID-19 patients are predisposed to developing fungal infections during the course and also in later stages of this disease, especially severely ill ones, due to a decrease of CD4 + T cells and CD8 + T cells leading to immune suppression.

There are various countries with many shortages in their medical and social systems in such settings severe progressions of osteomyelitis involving the jaws are still oftentimes discovered [8, 9, 10].

Despite all the advantages related to the advances in drugs and medicine, there are chances of development of resistance against commonly used antibiotics. There is an increase in number of patients taking steroids and alternative immunocompromising medicine, with rising incidence of AIDS, diabetes, and alternative medically compromising conditions leading to new problems within the treatment of osteomyelitis of the jaws, radiotherapy resulting in osteoradionecrosis has been a condition that, if super-infected, has contributed to an outsized range of difficult osteitis cases within the past decades. Recently, increasing range of patients treated with bisphosphonates are noted to develop osteonecrosis of the jawbone. This condition is called osteochemonecrosis.

CLASSIFICATION

There are many different classifications that are either based on the etiology, pathogenesis, pathologic or anatomic differences, the clinical course of the disease, or radiologic patterns. This makes a comparison between different studies very complicated or impossible. The Zürich classification [11] differs between three different kinds of osteomyelitis: The acute osteomyelitis, the secondary chronic osteomyelitis, and the primary chronic osteomyelitis (Table 1). The secondary chronic osteomyelitis results from the acute osteomyelitis and therefore is the same disease at a different time stage. Once the osteomyelitis persists

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for more than 4 weeks, it is defined as chronic [11].

Zürich classification [4]	**Different types of osteomyelitis**
Acute osteomyelitis Secondary chronic Osteomyelitis	Neonatal osteomyelitis Trauma-associated osteomyelitis Odontogenic osteomyelitis Foreign body-induced osteomyelitis Osteomyelitis based on a bone disease Osteomyelitis based on a systemic condition • Diabetes • Autoimmune diseases/ immunosuppression • AIDS • Agranulocytosis • Anemia • Leukemia • Syphilis • Malnutrition • Cancer/chemotherapy • Alcohol/tobacco/drugs • Herpes zoster/Cytomegaly
Primary chronic Osteomyelitis	Juvenile chronic osteomyelitis Adult onset osteomyelitis Syndrome associated • SAPHO • CRMO

Table 1 This table presents the Zürich classification of osteomyelitis on the left-hand side. In the right column are the different kinds of osteomyelitis that are included in the respective group of the Zürich classification [11]

Mucormycosis previously known as zygomycosis also known as black fungus, white fungus which resembles Candidiasis, Green fungus is Aspergillosis and Yellow fungus, also called mucor septic.

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'There are various types of fungal infections such as candida, aspergillosis, cryptococcus, histoplasmosis and coccidioidomycosis. Mucormycosis, candida and aspergillosis are the ones observed more in those with low immunity,"

EPIDEMIOLOGY

Approximately 17% of all osteomyelitis cases belong to the group of the acute osteomyelitis, 70% to the secondary chronic osteomyelitis, and 10% to the primary chronic osteomyelitis [11]. The average age at the time of diagnosis is a little bit over 40 years for the acute and the secondary chronic osteomyelitis [11]. Because of the inhomogeneity of the secondary chronic osteomyelitis, a general age group cannot be given. The etiology of the primary chronic osteomyelitis is an infection of unknown origin [11].

The incidence ratio of osteomyelitis of the maxilla to the mandible ranges from 1.07:1 to 1:6.5. [14,15] In the present antibiotic era, osteomyelitis of the facial bones is a rare condition. The incidence of osteomyelitis involving the maxilla is 45.1%, as reported by Koorbusch et al [15].

Pathogenesis

The acute osteomyelitis and secondary chronic osteomyelitis are caused by a local infection due to bacteria from the oral cavity. The likelihood of the development of the infection depends on the virulence and number of bacteria and the quality of the local immune response and the blood flow [11]. Therefore, general diseases affecting the immune system are risk factors in the development of osteomyelitis, e.g., diabetes, autoimmune diseases, or anemia. A typical course of the acute and secondary chronic osteomyelitis is the contamination of the bone with bacteria. The bacteria proliferate and colonize the bone marrow and reach via the Haversian and Volkmann canals to the periosteum. The edema under and in the periosteum disturbs the blood flow resulting in ischemic bone parts and potentially sequestrum building.

Fungal infection can be pathogenic or opportunistic. A pathogenic infection arises in a host with normal immune function, whereas an opportunistic fungal infection occurs in an immunocompromised, low-virulence host. Pathogenic fungal infections include histoplasmosis, blastomycosis, paracoccidioidomycosis, and coccidioidomycosis. These are infectious but not contagious. Saprophytic opportunistic fungal infections include mucormycosis, candidiasis, aspergillosis, cryptococcosis, and pneumocystis. The incidence of fungal osteomyelitis of the

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maxilla is 52%, the male-to-female ratio is 2.1:1.

Mucormycosis is an uncommon acute opportunistic infection caused by a saprophytic fungus that belongs to the order Mucorales, family Mucoraceae, and class Zygomycetes [16]. It was first described in humans by Paultaufi in 1885, as cited by Marchevsky et al [17]. The genera of Mucorales that are recognized as human pathogens are Rhizopus, Absidia, Rhizomucor, and Mucor. These organisms are frequently found to colonize the oral mucosa, nasal mucosa, paranasal sinuses, and pharyngeal mucosa in asymptomatic patients [18,19].

The above-mentioned fungus invades the arteries and forms thrombi within the blood vessels that reduce the blood supply and cause necrosis of the hard and soft tissues [20,21]. Once it has entered the arteries, the fungus can spread to orbital and intracranial structures [22,23]. Mucormycosis presents as an acute infection and manifests in a rhinocerebral, pulmonary, gastrointestinal, cutaneous, or disseminated form. [20] It is associated with comorbidities such as uncontrolled diabetes mellitus, is acidotic, and occurs in patients with hematologic malignant disease such as leukemia [24] or patients receiving immunosuppressive therapy. [24-25]

Histology

The acute osteomyelitis and the secondary chronic osteomyelitis are characterized by an inflammatory exudate, primary in the medullary spaces with fibrin, leucocytes, and macrophages that replace the fatty tissue and hematopoietic marrow. In addition, necrotic debris and bacteria can be found [11, 12]. The most common bacteria being detected is Staphylococcus aureus (85%) [11]. Due to the blood flow disturbances parts of the bone becomes dead so that empty osteocytic lacunae can be observed. Sequestrae may be present. New bone formation under the periosteum is not uncommon. In cases of secondary chronic osteomyelitis, sequestrum formation is more common than in the acute osteomyelitis. The more chronic the course is, the more likely is the development of bone marrow fibrosis and sclerosis of the bone. Bacteria might be present. Actinomyces drusen are typical.

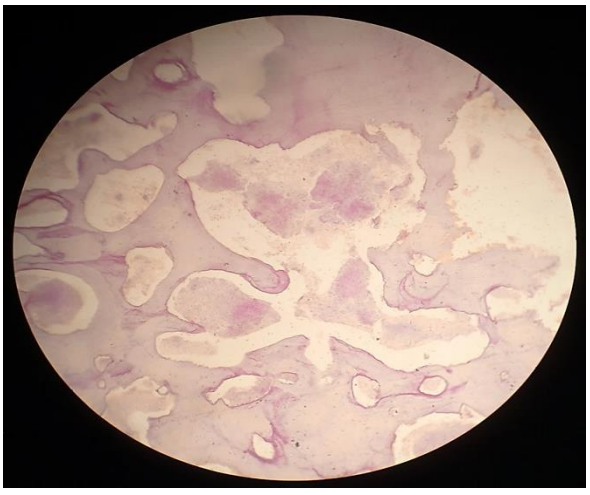

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Fig1- H&E stained Section of Lesional Tissue showing radiating appearance of actinomycese with central necrosis and surrounding host bone

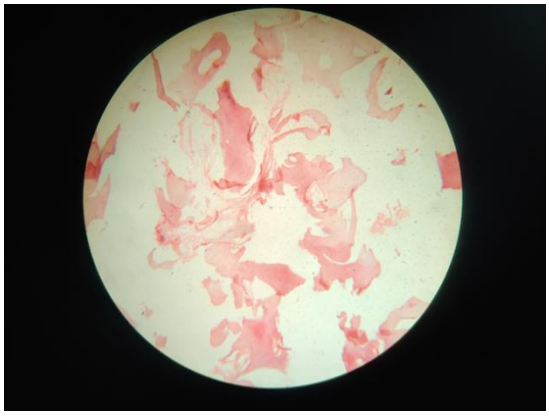

Figure 2- Photomicrograph showing Necrosed bone and bony lacunae

In the primary chronic osteomyelitis, plasma cells are predominant in the inflammatory infiltrate. The proportion of neutrophils, lymphocytes, and macrophages is rather small. The bone marrow is altered due to fibrosis. New bone formation is a common sign. Osteoclastic activity leads to repeated bone remodeling without a distinct histological bone formation pattern. Microabscesses might be observed [11].

Fungal hyphae produce ‘‘rhizoferrin,’’ which binds to serum iron. The rhizoferriniron complex is important for fungal growth. Hence, patients with diabetic ketoacidosis are more susceptible to mucormycosis as they have elevated levels of serum iron.

Symptoms

In cases of acute osteomyelitis, patients present with high fever and are listless. Local swelling can be observed with pain on palpation. The affected area is reddish, a trismus might be present, and quite often the teeth have higher mobility with pus coming out of the periodontium. If the inferior alveolar nerve is affected, patients report paresthesia of the lips (Vincent symptom). There are cases in which the symptoms are not very distinctive.

Symptoms of the secondary chronic osteomyelitis are the painful swellings that are usually not as prominent as in the acute osteomyelitis. A common finding is a periosteal reaction causing a solid swelling. Further symptoms are sequestrum formation and fistulas.

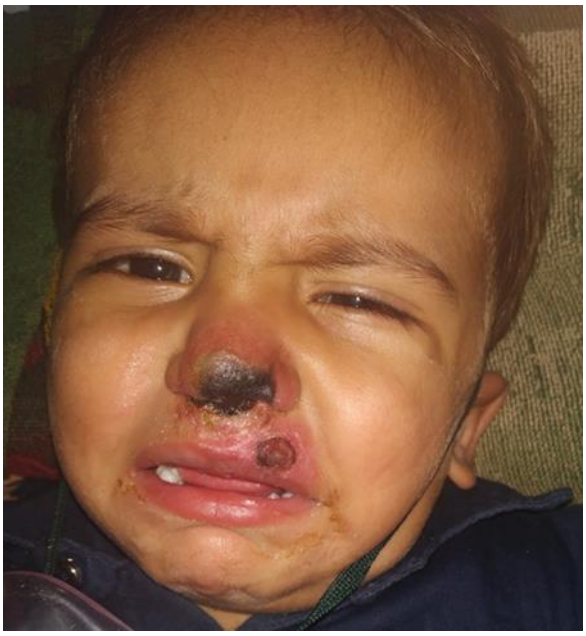

Fig 3- 1-year old boy with black fungus on his nasolabial region

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The primary chronic osteomyelitis is characterized by a nonsuppurative inflammation and sometimes only barely noticeable symptoms. In active periods, the patients notice pain, swelling, and mouth-opening limitations. Due to the bone formation, permanent swelling will develop eventually [11].

Symptoms of fungal osteomyelitis, involving the oral and craniofacial tissues account for about 60% of all cases.[20-23] Intraorally, the hard palate is usually affected because of its proximity to the infection of the nasal fossa, and the paranasal sinuses, alveolar mucosa, tongue, and buccal mucosa of the lips and cheek also may be affected. If left untreated, this condition will cause severe comorbidity with craniofacial deformity and death, which occurs at a rate of 66 to 70%. [20-23] multiple draining sinuses were also present intraorally.

COMPLICATIONS

A typical complication of the acute osteomyelitis is a shift into the chronic osteomyelitis that is very hard to treat sufficiently. Further complications are the development of the Vincent syndrome, fistula, abscess and sequester formation, and potentially fractures [11].

There are very severe complications of Covid such as Acute Respiratory Failure, Pneumonia,

Acute respiratory distress syndrome (ARDS) and Acute liver injury and many more. Some are associated with opportunistic infections also.

DIAGNOSIS

The diagnosis is based on the clinical course. This is completed by radiology: panoramic radiograph, cone beam CT, CT, or MRI. Changes in the bone can only be seen after a 30 to 40% reduction of the mineralized part of the bone. Therefore, the changes in the acute osteomyelitis are marginal at the beginning. In complex cases of osteomyelitis, a bone scintigraphy might be used to detect further active spots in the skeleton, e.g., in the diagnosis of chronic recurrent multifocal osteomyelitis or the SAPHO syndrome (SAPHO: Synovitis, acne, pustulosis, hyperostosis, osteitis) [13]. Radiological signs of acute osteomyelitis are: Bone resorption with increased radiolucency, loss of spongious structure of the bone, potentially sequester formation. Radiological signs of the secondary chronic osteomyelitis are: Bone resorption with increased radiolucency, sequester formation, periosteal reaction, and pathological fractures. Radiological signs of the primary chronic osteomyelitis are: Increased radiopacity with loss of trabecular bone, bone resorption, and periosteal reaction [11].

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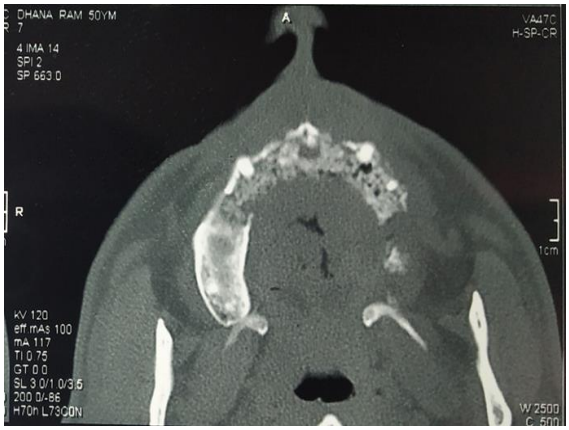

Fig 4: CT scan revealed that the axial view showed an extensive mixed density lesion involving the left alveolar process of maxilla with a moth-eaten appearance.

The diagnostic workup is of paramount importance to differentiate between bacterial and fungal osteomyelitis. Routine blood investigations show leucocytosis in the 12,000/mL to 20,000/mL range and a Schilling shift to the left. The biopsy specimens of bony tissues in decalcified sections show irregular bony trabeculae with empty osteolytic lacunae. The presence of fungal hyphae within the bone suggests the fungal nature.

Culture and sensitivity testing should be performed in all cases irrespective of the nature of osteomyelitis. All histopathologic sections should be stained with hematoxylin-eosin on a 10% potassium hydroxide mount, periodic acid–Schiff, and Gomori methenamine silver stain. Gomori methenamine silver stain specifically identifies the nature of hyphae, whether septate or aseptate. Identification can be accurately performed on the histopathologic sections themselves, and the culture on Sabouraud agar will yield a ‘‘cotton-candy appearance’’ thus confirming the exact species.

Differential Diagnosis

In the differential diagnosis, one should rule out malignancies in unclear cases so that biopsies should be performed. Culture of specimen plays an important role in this.

Therapy

The therapy of the acute and secondary chronic osteomyelitis along with fungal osteomyelitis mainly includes the therapy of the infection and of the improvement of the local blood flow. This is achieved via antibiotics and removing of the infected parts of the bone. A decortication supports this and helps to get well-vascularized tissue onto the bone. Acute osteomyelitis is immediately treated with Antibiotics.

If an antibiogram suggests different antibiotics, an adaptation should be performed after the initial anti-microbiological therapy. Mouth rinses, hygiene, and cold application can be applied. In general, the highly mobile teeth should not be extracted since they will gain stability again after the acute stadium of the osteomyelitis is over.

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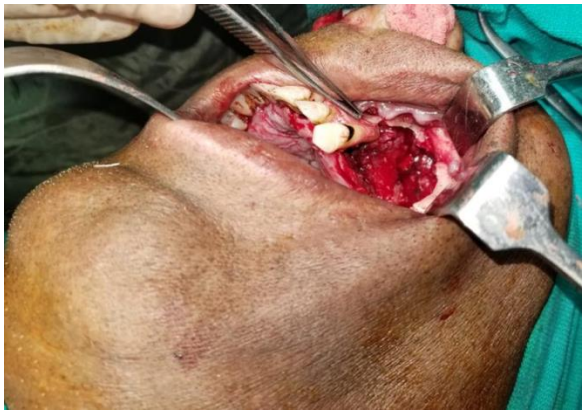

Fig 5- shows intraoperative view of the maxilla after removal of the sequestrum

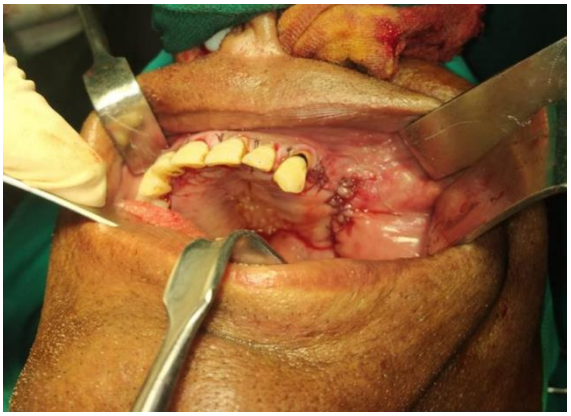

Fig 6- shows primary closure with aid of buccal advancement flap

The therapy of the secondary chronic osteomyelitis aims at sufficient pain management, limitation of the spread of the affected areas, fracture prevention, and the prevention of the onset of further active periods. Secondary diseases such as diabetes need to be treated as well. The therapy of the primary chronic osteomyelitis consists of a surgical intervention to remove the necrotic bone parts and a potential disfigurement can be corrected. But recurrences of the symptoms are very common. Therefore, other treatment options should be used as well including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDS), steroids, and bisphosphonates (mainly pamidronate). According to Topazian et al 14 days of empirical antibiotic should be given in cases of osteomyelitis.

The preoperative preparation for fungal infections like mucormycosis which included 2 doses of 50 mg of lyophilized amphotericin B under a strict intensive care unit setup with all parameters in place, given its high incidence of nephrotoxicity and allergic reaction potential. All the patients received the antifungal therapy intravenously, which was diluted in 500 mL of normal saline solution at a rate of 50 mL/h initially for 15 minutes and then increased to 250 mL/h. Because of renal toxicity associated with amphotericin- B therapy, it should be changed to new formulations of the drug which would be less nephrotoxic such as Liposomal amphothericin- B (LAT-B), amphotericin-B colloidal dispersion or lipid complex [26]. For this reason, we preferred the LAT-B therapy initially. LAT-B tolerance is excellent and results only minor increase in the serum creatinine level during the period of therapy [27].

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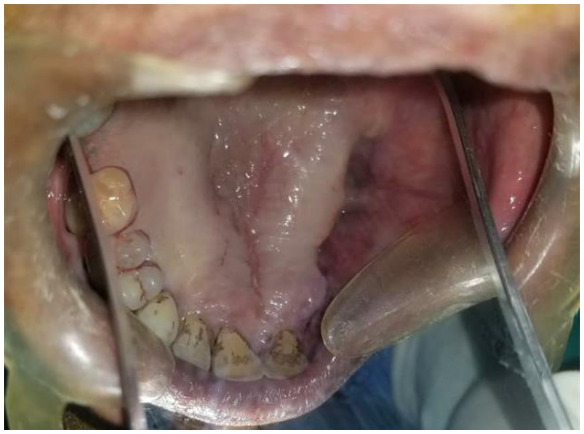

Figure 7 – mirror image showing loss involvement of maxillary bone

Second line- AZOLE Derivatives (Step Down or Salvage Therapy): Posaconazole is broad-spectrum azoles available in both parenteral and oral formulations can be used.

All this has to be continued till resolution of initially indicative findings on imaging and reconstitution of host immune system.

Reconstruction is always possible only after ruling out the amount of healthy bone which is left for support for reconstruction. Primary reconstruction can be done with flap closure/ placing obturator and later it can be reconstructed with the help of placing implants.

PROGNOSIS

The therapeutic success is higher in patients with acute and secondary chronic osteomyelitis than in patients with primary chronic osteomyelitis. Approximately 75% of the acute and secondary chronic osteomyelitis are symptom-free after intervention whereas only about 25% are symptom-free of the patients with primary chronic osteomyelitis [11].

Mucormycosis has been found to be associated with poor prognosis & with higher mortality rate. Mortality is higher in cases of patients who have delay in diagnosis for more then 2-4 days.

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