Bacterial Osteomyelitis versus Diffuse Sclerosing Osteomyelitis of the jaw, similar nomenclature, different disease entity

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To Damascus, the city living inside me
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1. Introduction

1.1 Definition of the disease

Osteomyelitis (OM) is a true bacterial infection associated with inflammation of the bone marrow, the overlying cortical plates and periosteum. The infection can be limited to a localised section of the bone or can involve several different regions such as the bone marrow, cortex, periosteum or even extend to the surrounding soft tissue (Harik & Smeltzer, 2010). The clinical term osteomyelitis is derived from Greek, with osteon meaning bone, myelos standing for marrow, and itis, a suffix used in pathological terms indicating an infection of a specific part of the body (Malhotra, Chan, & Nather, 2014).

Osteomyelitis of the jaw can be distinguished from long bone osteomyelitis in several important ways, mainly due to its specific features where the bone of the jaw is connected to the oral cavity, teeth and periodontal membrane (M. M. Baltensperger, Eyrich, & SpringerLink (Online service), 2009). During the course of the disease, the affected bone does not heal and remains exposed in the mouth even after appropriate intervention (Reid, 2009).

Albeit the improvements in dental care, osteomyelitis of the jaw is still considered one of the most challenging problems for dental clinicians and maxillofacial surgeons. The introduction of antibiotics in the twentieth century has decreased the risk of acquiring the disease and its complications significantly (Hudson, 1993; Goda, Maruyama, Michi, Nakagawa, and Harada (2014); (Lu et al., 2016).

The patient’s history, clinical and radiological examinations as well as intraoperative findings are the cornerstones for diagnosing OM (Nezafati, Ghavimi, & Yavari, 2009). Histological and microbiological tests also play a major role (Dimitrakopoulos, Magopoulos, & Katopodi, 2007; Senel, Jessen, Melo, & Obeid, 2007). Radiation, malignancy, osteoporosis and other factors impairing blood supply or inducing necrosis by altering the bone vascularity are considered predisposing factors of the disease. Diabetes may have a serious influence on the course of OM as it alters the host defence mechanisms (Topazian & Binder, 1994). Medications most commonly associated with OM are steroids and chemotherapeutic agents (Esenyel et al., 2007; Reid & Cundy, 2009; Yavuz, Kaya, Yalcin, & Aras, 2008).
1.2 Classification of osteomyelitis

From a practical point of view, distinction of the different types of osteomyelitis is useful (Kwon, Choi, Ahn, & An, 2013; Lew & Waldvogel, 2004). Baltensperger and Eyrich reviewed osteomyelitis of the jaw in the literature and differentiated precisely between many classifications of the OM based on clinical pictures, aetiology, radiology, pathogenesis, pathological anatomy, and pathophysiology (M. M. Baltensperger et al., 2009). There are numerous suggested classification systems of OM in the literature, which has led to the absence of an international consensus nomenclature and confusion regarding the results of comparative studies.

One of the important classifications divides OM into bacterial osteomyelitis (B-OM), including acute, chronic suppurative and secondary chronic OM caused by bacterial odontogenic infection or haematogenous spread, and non-bacterial osteomyelitis (NB-OM), which is used as an umbrella term describing non-infectious inflammatory bone disorders where the cause remains unidentified. NB-OM includes diffuse sclerosing osteomyelitis (DSO), chronic recurrent multifocal osteomyelitis (CRMO), primary chronic OM, sclerosing non-suppurative OM and SAPHO (synovitis, acne, pustulosis, hyperosteitis and osteitis) syndrome (Suei, Taguchi, & Tanimoto, 2005) (Supplementary Table 1).

1.3 Aetiology of the disease

1.3.1 Bacterial osteomyelitis (B-OM)

Bacterial osteomyelitis of the jaw is caused by infections derived from a wide range of microorganisms such as bacteria, mycobacteria, fungi, viruses and parasites (Gabrielli et al., 2014). The most common bacterial organism responsible is Staphylococcus aureus, followed by haemolytic streptococcus, pneumococcus, Escherichia coli, and Proteus species. An infection caused by two or more of these bacteria has also been well documented (Sun, Xue, Wu, & Zhou, 2017).

The presence of teeth plays a vital role in the disease aetiology by providing the bacteria with a direct pathway to the bone, this invasion of the bone in turn causes the development of osteomyelitis. This leads to pervasive inflammation, necrosis and bone
destruction at the sites of infection. Smoking, diabetes, anaemia, malnutrition, malignancies, immunocompromised status as well as other systemic factors causing bone hypovascularity can predispose to OM (Baur, Altay, Flores-Hidalgo, Ort, & Quereshy, 2015; Ehrenfeld, 2000; Kwon et al., 2013; Lu et al., 2016; Rosenberg & Khurana, 2016; Sun, Xue, Wu, & Zhou, 2016). Avital and impacted teeth as well as periodontal diseases have been implicated as possible OM triggering factors (Calhoun, Shapiro, Stiernberg, Calhoun, & Mader, 1988; Koorbusch, Fotos, & Goll, 1992; Neumann, Steinbrecher, & Thimann, 1975). It was also observed that the bacteraemia occurring after extractions and mucogingival procedures plays a role in the pathogenesis of the acute OM (Otten, 1987).

Osteoradionecrosis, or radioosteomyelitis, is a special form of bacterial osteomyelitis (R. E. Marx, 1983) in which irradiation of the bone leads to the formation of transcribed necrosis. Vascular damage causing bone hypovascularity has been implicated as the aetiology behind this entity (Ehrenfeld, 2000; Robert E. Marx & Ames, 1982). In addition, during fixation and open reduction of bone fragments, when the fracture edges are not stabilised against each other, in combination with the above mentioned reduced systemic factors may result in the development of a specific type of bacterial osteomyelitis called trauma/fracture-related acute osteomyelitis (in German: Bruchspaltosteomyelitis). This type of OM sometimes occurs after orthognathic surgeries, and the reported infection rate in these cases is up to 17.5% (Düker, 2000). Furthermore, the risk of infection during intra-oral operations and osteotomies due to saliva contamination is always present.

Bacterial osteomyelitis is divided into acute and chronic forms (Zimmerli & Fluckiger, 2004). The acute form of bacterial osteomyelitis is differentiated from the chronic form by its rapid onset, usually the infection is diagnosed within two weeks after initiation of the disease and it is usually highly acute. When the diagnosis persists for more than two weeks after the appearance of symptoms the sub-acute type will be diagnosed (Bohndorf, 2004). The term secondary chronic osteomyelitis refers to when the complaint lasts for several months after the acute form, the transition from the sub-acute to the chronic form is smooth, with no clear separation between the two phases
The chronic form of osteomyelitis is classified based on the aetiology into two forms:

- Exogenous chronic osteomyelitis in which mandibular exogenous chronic osteomyelitis, occurring after an extended infection from a nearby soft or hard tissue (Loh & Ling, 1993), can be differentiated from the exogenous chronic osteomyelitis of the long bone, happening post-trauma or post-operatively.
- Endogenous chronic osteomyelitis involving haematogenous infection (Bass, 1928; Engel, 1939; Heslop, 1956; Lacey, 1929; Nade, 1983; Rowe, 1956).

The transition from acute to chronic haematogenous OM occurs due to reduced immunity or inadequate treatment of the acute phase (Bohndorf, 2004). This type of OM is very rare and occurs only in infants and young children in the form of infantile osteomyelitis (Graswinckel, Marti, & Besselaar, 1988).

1.3.2 Non-bacterial osteomyelitis (NB-OM)

Another clinical entity of the so-called osteomyelitis is diffuse sclerosing osteomyelitis (DSO), a chronic non-bacterial disease with low grade infection and unknown aetiology (Hino, Murase, Terakado, Shintani, & Hamakawa, 2005; Otto et al., 2015), exclusively affecting the mandible. The aetiology and pathogenesis of DSO remain controversial. Many studies in the literature believe it is a response to a microbial stimulus of low virulent bacteria (M. Baltensperger et al., 2004; Eyrich, Baltensperger, Bruder, & Graetz, 2003; Eyrich et al., 1999; Eyrich, Langenegger, Bruder, Sailer, & Michel, 2000), but a specific microbiome has not been identified (Montonen & Lindqvist, 2003).

Some authors support the hypothesis of an autoimmune process causing the disease (Khanna, Sato, & Ferguson, 2009) and that the inflammatory response could be due to a hyperactive immunologic reaction to the bacterial toxins (Kuijpers, de Jong, Hamdy, & van Merkesteyn, 2011; Montonen, Kalso, Pylkkaren, Lindstrom, & Lindqvist, 2001; Montonen & Lindqvist, 2003). Others have introduced chronic periostitis as a new concept of its aetiology. Furthermore, it has been also suggested that DSO is due to chronic muscular hyperactivity (van de Meent et al., 2017).
1.4 Histopathology of osteomyelitis

1.4.1 Bacterial osteomyelitis (B-OM)

Many microscopic as well as macroscopic changes occur throughout the various stages of osteomyelitis. An increase in the intramedullary pressure causes the death of the central soft tissue, with the pus-forming infection spreading through the bone marrow and the canals. Septic thrombosis causes irreversible ischemic damage to the osteocytes and osteoclasts, leading to necrosis of large parts of bone and prevention of bone remodelling. The formation of granulation tissue in addition to the increase in osteoclastic activity, occurring at the border between the dead and still viable bone, causes the detachment of the necrotic sequester, which in turn lies loosely in the centre. A surrounding zone of fibrotic and reactive bone layer coats the granulation tissue, completely walling off the necrotic infective part. If this thickened new bone fails to compartmentalise the infection, dissemination through the whole bone marrow and even an extramedullary spread may occur. This leads to the periosteum reacting with the newly formed bone around outbreak areas. The immune defence reaction depends on the general status of the immune system as well as that of the blood vessels (Ehrenfeld, 2000).

A biopsy can be used to verify the histopathological findings. In the case of acute osteomyelitis, necrotic bone tissue with osteocyte loss, peripheral resorption, bacterial colonisation, and infiltration of polymorphic leukocytes, a sign of acute inflammation, are the main features (Schimming, 2003). In chronic osteomyelitis, there is evidence of resorptive, necrotising as well as regenerative bone processes (Evers, 1978; Sitzmann, 2003a). Nonetheless, differentiation of chronic osteomyelitis according to the histology alone is not enough, rather acknowledgement of all findings including follow-up is necessary to reach a correct diagnosis (Ehrenfeld, 2000).

1.4.2 Non-bacterial osteomyelitis (NB-OM)

Histological biopsy results demonstrate a non-specific chronic inflammation, indicated mainly by infiltration of plasma cells, with varying amounts of neutrophils, lymphocytes, and macrophages (M. Baltensperger et al., 2004; Frid, Tornes, Nielsen, & Skaug, 2009). Medullary fibrosis is the most common characteristic of advance disease along with endosteal bone apposition with pagetoid (irregular of reversal lines) reaction. These findings
are also frequent in elderly patients. The development of subperiosteal bone and absorption of the bone are more prominent in early stages of the disease and in younger patients (M. Baltensperger et al., 2004). Although further studies are needed, increased accuracy can be achieved by extra-oral sampling or polymerase chain reaction (PCR) (Frid et al., 2009).

1.5 Diagnosis

1.5.1 Medical history

The medical history or anamnesis should be attained by asking exact questions, with the aim of gaining information helpful in achieving a diagnosis or a provisional diagnosis of the disease.

1.5.2 Clinical signs and symptoms

These include intra and extra-oral examination, such as inspection, palpation, nerve sensibility tests and teeth vitality tests.

*Bacterial osteomyelitis (B-OM)*

Osteomyelitis of the jaw is one of the most difficult inflammatory diseases in the head and neck region, the earlier it is diagnosed, the easier it is to treat with less complications, but diagnosis in early stages is challenging because it differs depending on the level of infection, localisation of the disease, patients’ resistance and age (Karmazyn, 2010).

Acute bacterial osteomyelitis is characterised by the classical symptoms of infection, like impairment of general conditions, severe pain, fever, swelling, redness and warmth at the affected site, and may show a suppurative course with abscess, as well as cervical lymphadenopathy with a moderate risk of sepsis which is associated with elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and pronounced leucocytosis (De Boeck, 2005; A. F. Jansson et al., 2009). Halitosis can occur caused by anaerobic bacteria, tooth mobility, leading to malocclusion (AWMF-Leitlinien, 2002). Usually acute bacterial OM resolves completely with adequate treatment, but sometimes due to inadequate antibiotic regime, it can transform into chronic osteomyelitis (Harik & Smeltzer, 2010).
A clinical presentation similar to acute bacterial OM is usually witnessed with chronic bacterial osteomyelitis, although it remains remarkably milder and often associated with recurrent pain and swelling without the manifestations of the acute infection. Chronic B-OM is characterised by exposed necrotic bone with sequester formation, tooth mobility, fistula formation with pus discharging through the gingival sockets, and when the mandible is also involved, hypoesthesia of the lower lip (Vincent’s symptom) and trismus may also develop (Sasaki & Nameta, 1994). Fistula formation and the attempt to drain the accumulated exudate through it, is a well-known feature of the chronic phases of any infection. If the fistula becomes obstructed or any obstacle arises hindering the draining of exudate, fever and elevation of inflammatory parameters will be observed, similar to the acute phase (Schilli, 1988; Schimming, 2003). Limited jaw function due to inflammation of temporomandibular joint and/or infection of the masticatory muscles could also occur. Pathological fracture of the jaw is expected in bacterial OM, arising due to resorption or surgical removal of necrotised tissue, which will then be replaced by granulation tissue, weakening the bone (Schilli, 1988).

*Non-bacterial osteomyelitis (NB-OM)*

Primary chronic osteomyelitis, diffuse sclerosing osteomyelitis, as well as other types of non-bacterial OM, can remain clinically silent in the early stages of disease. Later, and in some active episodes of the disease, pain, swelling of the soft tissue, bone deformities as well as some of the features of the B-OM can develop (Schimming, 2003). In the symptomatic period, blood tests usually reveal normal values of leukocytes, ESR and CRP, while the asymptomatic period can sometimes be associated with elevated levels of these parameters. For this reason, a diagnosis of a non-bacterial osteomyelitis should not depend on the blood results (Schmailzl, 1995). Recurrence of symptoms is frequently recorded in many studies. Indeed, Montonen *et al.* (1993) reported that the symptoms of 75% of the treated cases recurred, especially mild pain, Vincent’s symptom and swelling of the soft tissue. Sudden deafness, an extremely rare complication of non-bacterial OM localised in the temporomandibular joints (TMJ), has also been reported (Marsot-Dupuch, Doyen, Grauer, & de Givry, 1999).
1.5.3 Diagnostic imaging

As previously mentioned, the diagnosis of the acute as well as chronic osteomyelitis should not depend only on clinical features, physical examination or laboratory findings, but also on radiological examination, an x-ray should always be performed when OM is suspected (Khanna et al., 2009). Diagnostic radiological imaging plays a vital role in differentiating OM from other diseases with similar features, such as tumours and fractures (Lalam, Cassar-Pullicino, & Tins, 2007).

Several radiological techniques, including conventional radiograph, cone beam computed tomography (CBCT), computed tomography (CT), skeletal scintigraphy and magnetic resonance imaging (MRI), can be used to assist in confirming a diagnosis of OM, recognising the source of the infection, detecting the extensions and localisation of the lesions as well as verifying the involvement of the soft tissue around the lesions (Boeddinghaus & Whyte, 2017; Harik & Smeltzer, 2010). The use of ultrasonography to detect signs of change in the bone marrow is not enough to reach a diagnosis of OM, but rather the detection of indirect signals, such as changes of the surrounding soft tissues, should be used to verify the diagnosis (Bohndorf, 2004).

Conventional radiology

The orthopantomogram (OPT), or dental panoramic tomography (DPT), is considered to be the gold standard imaging tool. It offers a clear view of the maxilla, mandible, and the TMJ simultaneously and in one plane. OPT advantages of being affordable and readily available in most dental clinics and institutions add to its superiority. Nowadays, most panoramic devices are digital, producing a good overview at a low effective dose of 4.7 to 6.2 µSv (Gijbels et al., 2005; Ludlow, Davies-Ludlow, & Brooks, 2003). The older analogue types require a markedly higher dose, ranging between 16 and 26 µSv (Visser, Hermann, Bredemeier, & Kohler, 2000). Conventional imaging techniques are sometimes required to clarify some anatomical regions, such as the posteroanterior (PA) view, bilateral oblique views, Towne view, and water view.

In the case of chronic OM, conventional radiology shows the sequester as a radiopaque mass, surrounded by blurry, ill-defined osteolytic frame (Ehrenfeld, 2000; Schimming, 2003). It has been stated that the radiographic changes are seen only after
the loss of 30-50% of inorganic bone substance. For this reason, it takes at least 10-14 days from the onset of the disease for the first radiological sign to appear, since the newly formed bone requires a period of about 10 days, and the massive sclerotised bone needs 30 days to develop (Korner, Kreusch, Bohuslavizki, Brinkmann, & Kohnlein, 1997). Due to the fact that the discernibility of the disease with the use of OPT requires consequential changes in the mineral content of the bone, found only in chronic OM (Epstein, Rea, Wong, Spinelli, & Stevenson-Moore, 1987), MRI should be used in the diagnosis of early stages of OM, due to its ability to detect soft tissue changes as well as the bone oedema (McQueen, Lassere, & Ostergaard, 2006).

The limitation of the conventional radiology by demonstrating periosteal new bone deposition and bone destruction as an osteolytic and osteosclerotic lesions only, gives rise to the challenge of being able to differentiate between OM and its types from an inflammatory process caused by a neoplasm (Khanna et al., 2009). Radiological signs in the conventional radiology can be used to differentiate between bacterial and non-bacterial OM (M. M. Baltensperger et al., 2009). Destruction of the cortical bone with sequester formation, the presence of pathological fractures, densified periosteal reaction, as well as an increased radiolucency (in acute disease) or an increased radiopacity (in chronic disease) are all signs associated with bacterial OM. In contrast, non-bacterial OM is characterised by infrequent periosteal reaction, small radiolucent spots, as well as TMJ involvement.

**Computed tomography (CT)**

Computed tomography CT was invented and introduced into medical field in 1973, as an x-ray method utilising ionizing radiation (Hounsfield, 1980). Also known as cross sectional imaging, CT can impressively confirm the destruction of bone structure, show calcified periosteal reactions, and detect sequester, one of most important indications of a CT scan (Sitzmann, 2003b). CT scan does not allow the superimposition of anatomical structures. It also aides in the easy recognition of bony lesions more than an orthopantomogram. The presence of soft tissue inflammation can be observed, but a higher dosage of radiation is required (Sitzmann, 2003b; Spitzer, 1997). The effective dose of the CT scan needed for the mandible is about 480 µSv, while that for the maxilla is 580 µSv (Mah, Danforth, Bumann, & Hatcher, 2003).
Cone beam computed tomography (CBCT) has recently become one of the most reliable three-dimensions (3D) imaging technique in dentistry, acting as another option for the use of CT, especially in the head and neck area (Sukovic, 2003). The main advantage of CBCT over CT is the diminished effective dose of radiation, which is markedly lowered to almost 19.9 µSv for the maxilla and 34.7 µSv for the mandible (Akinmoladun, Akintububo, Adisa, Ojo, & Ayuba, 2013; Mah et al., 2003; Yu et al., 2009). Reduced image quality caused by artefacts generated by metal dental fillings, such as amalgam, is considered a disadvantage of both CT and CBCT.

In addition to the above mentioned radiological characteristics, CT-scans further aid in distinguishing between both disease entities (M. M. Baltensperger et al., 2009). Fistula and abscess formation, the presence of small areas of bone sclerosis with increased bone density, as well as demineralisation and erosion of the cortical plate are all observed in the acute phase of bacterial OM, while cortical plate thickening is usually observed in the chronic phase of the disease. Non-bacterial OM is marked by an increase in the size of the mandible, the presence of small osteolytic spots indicating infectious lacunae, destruction of the bone trabecular structure, mild bone growth, in addition to the infrequent finding of periosteal reaction.

*Magnetic resonance imaging (MRI)*

MRI is a highly sensitive and simultaneous non-invasive imaging technique, with no emission of radiation (Chung et al., 2002). It is considered as the imaging method of choice for the diagnosis and follow-up of OM and its progress (Jurik, 2004; Jurik & Egund, 1997). The ability to show high tissue contrast and great anatomical resolution in all three planes, coronal, axial and sagittal, are the main advantages of MRI (Bachmann, Jurgensen, Leiers, & Rauber, 1996). The accuracy of MRI in diagnosing acute OM reaches up to 94%, while it ranges from 80-100% in chronic cases (Spitzer, 1997). By excluding characteristics of bacterial OM, such as marrow infiltration, sequestration, abscess, and fistula, the MRI is able to differentiate between the two types of OM (Robertson & Hickling, 2001).

MRI imaging with contrast agent administration, such as gadolinium, can be used to detect atypical bone morrow features, cortical bone destruction (Yoshioka et al.,
2000), as well as the degree of periosteal inflammation (Zebedin et al., 1998; Reinert et al., 1995) characterised by its thickness (Schuknecht, Carls, Valavanis, & Sailer, 1997). The lesions shown by MRI are larger than those detected by CT and scintigraphy (Reinert et al., 1995). In cases of infants and young children, sedation or general anaesthesia may be necessary. Evaluation of the extent of bone destruction or in cases where MRI is contraindicated, for example by uncooperative patients, the use of CT recommended (Karmazyn, 2010).

**Skeletal scintigraphy (bone scan)**

Bone scintigraphy is one of the most frequently performed diagnostic imaging techniques used in the evaluation of numerous pathologic disorders, including types and locations of inflammatory bone diseases, like osteomyelitis, primary bone cancers as well as metastasis, and some fractures not visible with the use of conventional radiology (Bahk, 2013).

Skeletal scintigraphy has a high sensitivity, reaching up to 95% in cases of acute osteomyelitis, but has a low specificity (Glaser et al., 1997). Bony pathological changes are detected earlier than in conventional imaging, since the blood flow and the osteoblastic activity reflect the process of new bone formation (Alexander, 1976). Approximately 15-25% of patients with metastases have normal findings with conventional radiology, but abnormal scintigrams, which can also detect diseases in their earliest stages (McDougall, 1979).

Scintigraphy is achieved by injecting a small amount of radioactive labelled substance intravenously, known as radioactive tracer, such as technetium-99m–labelled diphosphonates, followed by image implementation after 2-4 hours (Love, Din, Tomas, Kalapparambath, & Palestro, 2003). Superimposition of soft tissues, a disadvantage of skeletal scintigraphy, can be overcome using single photon emission computerised tomography (SPECT) (Bachmann et al., 1996).

**1.5.4 Laboratory diagnostics**

A blood test specific for osteomyelitis has not yet been developed. In the case of active OM, as in almost all inflammatory diseases, the ESR may be elevated. This test, used
together with other non-specific tests such as CRP, is used only to confirm the presence of an inflammatory process, but it does not provide accurate information about the localisation or the cause of inflammation. CRP helps in evaluating the response to the therapy implemented, and checking the outcome of the treatment (Fritz & McDonald, 2008).

1.6 Treatment of osteomyelitis

Due to the complex nature of OM, a wide range of management protocols depending on several factors, such as type, aetiology of the disease, general health of the patient, and the presence of infected soft tissue and/or exposed jaw bones, can be implemented. Consequently, surgeons face a great challenge managing OM cases. The ability to succeed in reaching a correct diagnosis and controlling any underlying diseases are pivotal in tackling the OM problem. Optimisation of systemic and aetiological factors, such as maintaining normal blood sugar levels, renal and hepatic functions, as well as stabilising fractures if present, in addition to quitting smoking and alcohol, are vital to the management of the disease. Patient cooperation is also necessary due to the long treatment process (Schimming, 2003).

1.6.1 Bacterial osteomyelitis (B-OM)

Eliminating the causative bacteria, preventing the spread of infection, and if possible, promoting the regeneration of hard and soft tissues, are the main goals of OM therapy (Schilli, 1988). Treatment of acute and chronic bacterial OM are mainly divided into conservative and surgical intervention. Conservative treatment options are always recommended in cases of early and simple lesions, including improvement of oral care, local irrigation, antibiotic therapy, photodynamic therapy (PDT), and hyperbaric oxygen (HBO).

Antibiotic management

Antimicrobial therapy, including bacteriostatic and bactericidal effects of the antibiotics, is regularly used to prevent and treat bacterial infection in acute and chronic osteomyelitis. Antibiotics should be started early and may be changed after results of an antibiotic sensitivity test. Amoxicillin/clavulanic acid is usually used initially, due to its wide spectrum against gram-positive bacteria such as Staphylococcus aureus.
*Streptococcus* and *Clostridium*, as well as gram-negative bacteria, like enterobacterial infection (Shah, Ramola, & Nautiyal, 2016).

Most antibiotics used are considered as an adjuvant therapy and will normally lead to healing associated with neovascularisation, due to the fact that the local blood flow is essential for successful outcomes (Mader, Cripps, & Calhoun, 1999).

**Antimicrobial photodynamic therapy (PDT)**

Antimicrobial photodynamic therapy (PDT) was introduced in the medical field in the last century. The concept of this so-called laser therapy is killing microorganisms by applying harmless dyes or a photosensitiser (PS) combined with gentle visible light in an oxygenated medium. The use of photodynamic therapy is beneficial in OM patients suffering from other comorbidities, as it helps to reduce the use of antibiotic therapy, whose long-term usage can be harmful due to the side effects. However, photodynamic antimicrobial chemotherapy is still considered as an adjuvant therapy and not an alternative for the antibiotal therapy in the treatment of OM (Kharkwal, Sharma, Huang, Dai, & Hamblin, 2011; Rajesh, Koshi, Philip, & Mohan, 2011) (Figure 1).
Figure 1: Surgical debridement of an osteomyelitis lesion, and disinfecting the lesion using the antimicrobial photodynamic therapy (PDT).

1: Exploration of an osteomyelitis lesion in the mandible through an extra-oral approach, 2,3: exposing the isolated sequester, which has been sent to histopathology for further examination, 4: Debridement of the area using a round bur, 5, 6: followed by disinfection using antimicrobial photodynamic therapy (PDT).
Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) is a systemic treatment option which enhances healing of infected and necrotic tissues by decreasing the associated hypoxia. This is achieved by exposing the patient to 100% oxygen in several sessions within a closed pressurised room. The chamber should be used for single patient or a multiplace room can be used for the treatment of several patients at the same time (Grime & Bryson, 2001; Moen & Stuhr, 2012).

HBO acts by increasing the dissolved oxygen level in the blood, which stimulates angiogenesis and capillary formation, helping to inactivate fibroblasts and macrophages (Beehner MR, 1983), in addition to having bacteriostatic and bactericidal effects (Mader, Adams, Wallace, & Calhoun, 1990). For these reasons, it is considered a good adjuvant therapy for osteomyelitis, and will only help when combined with proper management. HBO is usually implemented pre and post-surgically for OM patients by using a pressure of 2.4 x 10^5 pascal for 1 or 2 hours daily (Ehrenfeld, 2000; Fang, 2009; Schimming, 2003).

A study by Chin-En Chen on 14 patients suffering from refractory chronic osteomyelitis treated with HBO combined with surgical and antibiotic treatments, revealed a high rate of success (79%), with 11 of the 14 patients showing no recurrence of the infection. In addition, they reported no HBO related complications (C. E. Chen, Shih, Fu, Wang, & Wang, 2003).

In addition to the management of OM, HBO is used widely in the field of dentistry. It shows promising results in the treatment of aggressive periodontitis, it is used as an adjuvant therapy in irradiated jaws implantology, and even in the management of osteoradionecrosis.

Pregnancy, patients with uncontrolled hyperthermia, claustrophobia, upper respiratory tract infection and seizure disorder are contraindications to the use of HBO (Devaraj & Srisakthi, 2014; Kaur, Pawar, Banerjee, & Garg, 2012).
Local antibiotics

The use of local antimicrobial drugs in addition to systemic therapy has been used in the management of bacterial osteomyelitis, but not as a standard type of therapy for every case of OM (Hartley & Sanderson, 2003). The advantage of using local antibiotics lies in the release of the high concentrations of antibiotics in the infected area. Local antibiotics, such as tobramycin or gentamicin, are used regularly after completing the debridement of the infected area, before wound closure. Currently, there are several application methods of local antibiotics, such as irrigation or the use of antibiotic-impregnated acrylic beads, which are removed afterwards during the surgical intervention, before the final reconstruction (Chisholm, Lew, & Sadasivan, 1993).

Surgical treatment

Despite all the above mentioned adjuvant therapies, including antibiotics, complete surgical removal of the diseased part of the bone still remains the mainstay treatment of OM (Baur et al., 2015). Surgical debridement accompanied with antibiotic therapy is the most common approach in the management of bacterial OM (Marx R, 1991). The surgical treatment options range from simple incision and pus drainage to staged surgical debridement with reconstruction of hard and soft tissues. Complete removal of the bone sequester, as well as granulation and necrotic tissue, preserving the adjacent vital structures, help the lesion to heal properly, (Lew & Waldvogel, 2004; Rao, Ziran, & Lipsky, 2011), and improve the vascularisation of the remaining bone. The use of a healthy soft tissue graft covering the exposed bone promotes the healing process and gives a better outcome (Grime, Bowerman, & Weller, 1990).

The study conducted by van Merkesteyn concluded that a bacterial OM treatment protocol of local debridement and marginal resection, accompanied with a one-week parenteral antibiotic therapy followed by oral antibiotics, will lead to satisfactory results (van Merkesteyn et al., 1997). In cases where excessive debridement is necessary or those with an underlying pathological fracture, the use of reconstruction plates or maxillomandibular fixation (MMF) guarantee proper stability and ensure immobilisation of the surgical area, which assists in proper healing. Segmental resection
or a mandibulectomy may be considered when extensive debridement is suspected or gentle debridement is not sufficient (Marx R, 1991).

The question of the right timing for reconstructions, whether simultaneously or in a second stage, has been debated in the literature. Some authors recommend immediate reconstruction using either free autologous bone or vascularised iliac crest, while others report that a two staged reconstruction is safer to perform (Ioannides C, 1994; Marx R, 1991). However, in both scenarios, the most important factor for a successful management of the disease remains the proper and adequate debridement of the lesion.

Evaluation and assessment of the intra and pre operative CT or MRI as well as the clinical findings, such as osseous bleeding from resected margins, are necessary to determine and plan the extent of the mandible resection (Buchbinder & St Hilaire, 2006; Suh et al., 2010). Other techniques include intraoperative tetracycline bone fluorescence (Otto et al., 2016; Ristow et al., 2017) (Figure 2).

**Figure 2**: Surgical debridement of the lower jaw using tetracycline bone fluorescence.

### 1.6.2 Non-bacterial osteomyelitis (NB-OM)

The precise management of non-bacterial OM has still not been formulated (Eleftheriou et al., 2010). However, nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesic therapy are the most common medications used as a first-line therapy, which reduce the symptoms of the disease, as well as steroidal medications, which are also very helpful in relieving pain and swelling, especially when the NSAIDs are ineffective (Eyrich et al., 1999). Therefore, early diagnosis and differentiation of osteomyelitis will save patients useless and sometimes even harmful surgical interventions, as well as ineffective long-term antibiotic treatment.
Even though many studies revealed that long-term antibiotic therapy has no effect on the progression of NB-OM (A. Jansson, Golla, Schneider, Jansson, & Belohradsky, 2002; Schilling, 1998; van Merkesteyn, Groot, Bras, McCarroll, & Bakker, 1990), HBO promotes blood perfusion, enhances osteogenesis and neovascularisation, and helps in combination with surgical decortication to increase the vascularity and decrease the pressure in the medullary bone, hence it is indicated in the management of some cases of non-bacterial OM (Jacobsson & Hollender, 1980; Montonen & Lindqvist, 2003; Suei, Taguchi, & Tanimoto, 1997; Van Merkesteyn, Groot, Bras, & Bakker, 1988).

Nonetheless, all the previously discussed treatment protocols are generally unsatisfactory and will not lead to longlasting elimination of symptoms like continued pain, trismus and inflammation (Groot, van Merkesteyn, van Soest, & Bras, 1992; Kuijpers et al., 2011; Van Merkesteyn et al., 1988). Consequently, the use of corticosteroids, tumor necrosis factor-alpha (TNF-α) inhibitors, and also bisphosphonates are reported.

In the last 20 years, several articles have been published discussing the treatment of NB-OM with different kinds of bisphosphonates, whether it requires nitrogen or not and whether it should be applied intravenously or orally (Montonen et al., 2001; Compeyrot-Lacassagne, Rosenberg, Babyn, & Laxer, 2007; Hino et al., 2005; Kuijpers et al., 2011; Soubrier, Dubost, Ristori, Sauvezie, & Bussiere, 2001; Sugata, Fujita, Myoken, & Kiriyama, 2003; Yamazaki et al., 2007). The efficiency of bisphosphonates in treating NB-OM offers an overview into the possible underlying pathophysiology. Clinical and radiological features, characterised by new bone deposition and resorption occurring in a random manner, as well as the bisphosphonates mode of action, indicate that osteoclastic activity and osteoclast/osteoblast imbalance, affecting osteogenesis and osteolysis, has an important part in disease development (Otto et al., 2015).
1.7 Differential Diagnosis

The aim of this study is to differentiate between bacterial and non-bacterial types of osteomyelitis, with the latter being considered an important differential diagnosis for acute and secondary chronic OM (A. F. Jansson et al., 2009). Primary malignant bone tumours, as well as metastases, commonly originate from the prostate, kidney, lung, or breast cancers, in addition to tumour-like lesions, such as fibrous dysplasia, medication related osteonecrosis of the jaw (MRONJ), osteoradionecrosis (ORN), and ossifying fibroma are also important differential diagnostic considerations. Proper clinical, radiological and histopathological examinations can easily lead to definitive diagnosis of osteomyelitis. Therefore, harvesting biopsy specimens is necessary to distinguish and confirm the diagnosis (Eyrich et al., 2003; M. Baltensperger et al., 2004; Stern & Ferguson, 2013).
2. Purpose of the Study

Despite a large number of proposed classification systems for osteomyelitis, and the many definitions of osteomyelitis in the literature, no comprehensive nomenclature has been formulated and internationally acknowledged. Therefore, clinicians could not until now, follow universal guidelines regarding this disease.

The aim of the study was to demonstrate our clinical experience with osteomyelitis of the jaw and differentiate between bacterial and diffuse sclerosing OM in terms of clinical, pathological, radiographic and microbiological findings with the treatment strategy of each type of OM.

The specific objectives were to:

1. Identify a suitable patient cohort
2. Examine the above mentioned parameters retrospectively
3. Tabulate these parameters and unveil similarities
4. Investigate potential factors linked to the occurrence of OM of the jaw
5. Identify risk factors associated with OM
6. Develop a comparison between the types of OM based on etiological factors of osteomyelitis
7. Document the treatment methods of patients.
3. Patients and Methods

3.1 Study design and sample selection

This retrospective cohort study screened and analysed the medical records of patients with bone lesions who had been admitted to the Oral and Maxillofacial Surgery Department, Ludwig-Maximilians-University, Munich, Germany from 4th January 2003 to 30th December 2012, according to STROBE (Strengthening the Reporting of Observational studies in Epidemiology).

Inclusion criteria: patients with a clinically and radiologically confirmed diagnosis of osteomyelitis who had received conservative or surgical treatment.

Exclusion criteria: patients with a history of radiation to the head and neck region or if they had received antiresorptive drugs prior to the diagnosis of osteomyelitis (bisphosphonates or denosumab), either orally or intravenously.

3.2 Study variables

Data were gathered from the institution’s archive by screening patients’ records such as medical files, clinical photos, radiographs and operational reports.

The extracted data included:

- Demographic data (age, gender)
- Health issues and behavioural habits such as alcohol and alcohol consumption
- Underlying diseases
- Comorbidities and medications
- Risk factors
- Clinical findings
- Location of the lesion
- Radiological findings (panoramic radiograph OPT and/or cone beam CT and/or magnet resonance imaging)
- Information about their treatment
3.3 Ethics

The study design was reviewed and approved by the ethical committee of the medical faculty, Ludwig-Maximilians-University (Project-Nr. 083-11). The patient data was anonymous; none of the patients were submitted to any experimental trial of any kind. The need for patient informed consent was waived given the retrospective nature of the study.

3.4 Treatment protocol

Treatment was provided based on the treatment classification of the German Association of Oral and Maxillofacial surgery DGMKG (AWMF online, stand 2008). Conservative treatment consisted of irrigation and systemic antibiotics (amoxicillin/clavulanic acid 875/125 twice daily, or clindamycin 600 mg three times daily); some cases were treated with photodynamic therapy and hyperbaric oxygen therapy. Surgical treatment included incision and drainage, curettage, sequestrectomy, debridement of the necrotic bone, decortications, local application of antibiotics, extraction of causative teeth, splinting of movable teeth, microvascular reconstruction and fracture stabilisation.

3.5 Data analysis

The data were tabulated in Microsoft Excel (Microsoft, Redmond WA, USA) and were analysed with SPSS statistical software (SPSS Statistics Version 20, IBM). Descriptive and inferential statistics were computed with respect to the variable scale. Fisher’s exact test with Chi-square test were applied and results were written down in mean values and in percentages, standard errors of range and mean were included. The significance level was set at p < 0.05.
4. Results

The medical records of 175 patients who had been admitted to the Oral and Maxillofacial Surgery Department were screened, of which, a total of 67 patients diagnosed with OM were included in this study. Among them, 52 patients were suffering from B-OM and 15 from NB-OM (DSO). Figure 3 shows the percentage of the two types of OM.

![Diagram](image)

Figure 3: Flowchart of number of patients in the study.

Data were classified according to the following categories: age, sex, location of the lesion, distribution of the disease, comorbidities and medications, behavioural risk factors, clinical presentation, radiographic features and treatment.
4.1 Age and sex

The study sample consisted of 67 patients. The mean age of the patients diagnosed with OM was 51.8 years, with B-OM patients having a mean age of $55.4 \pm 19.5$ years. In general, the majority of patients were female (40 of the 67 patients; 59.7%). There was a female predilection in the ratio of 4:1 in NB-OM, however, the ratio of females to males was close to 1:1 for B-OM.

4.2 Location of the lesion

The mandible was the most affected site in B-OM (88.5%) and NB-OM (100%), whereas NB-OM was never present in the maxilla, but exclusively related to the mandible. One patient had the lesion in both jaws for B-OM (1.9%). Table 1 summarises the demographic data of both B-OM and NB-OM.

<table>
<thead>
<tr>
<th>Table 1: Descriptive statistics and results of the comparison of the demographic data of both groups of osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>( \leq 30 )</td>
</tr>
<tr>
<td>31 - 40</td>
</tr>
<tr>
<td>41 - 50</td>
</tr>
<tr>
<td>51 – 60</td>
</tr>
<tr>
<td>61 – 70</td>
</tr>
<tr>
<td>71 – 80</td>
</tr>
<tr>
<td>( \geq 81 )</td>
</tr>
<tr>
<td><strong>Location</strong></td>
</tr>
<tr>
<td>Maxilla</td>
</tr>
<tr>
<td>Mandible</td>
</tr>
<tr>
<td>Both</td>
</tr>
</tbody>
</table>

*: significant at \( P \leq 0.05 \)
4.3 Distribution of the disease

The distribution of the necrotic lesions was symmetric, with osteomyelitis occurring in the right side of the jaw accounting for 41.6% of the cases. The same result was observed for cases in the left side of the jaw (41.6%). In the remaining 14.9% of cases, both sides of the jaw were affected. Figure 4 shows an accurate description of affected areas (using the International dental scheme of FDI World Dental Federation).

![Figure 4: Distribution of osteomyelitis in the oral cavity based on the International Dental Scheme (FDI). Panel (A): Bacterial osteomyelitis (B-OM) and (B): Non-bacterial osteomyelitis (NB-OM; Diffuse sclerosing osteomyelitis of the jaw).](image-url)
4.4 Comorbidities and medications

Based on patients’ records, 6 of the 67 patients (5 patients with B-OM and 1 with NB-OM) were diagnosed with diabetes mellitus. Fifteen patients (28%) with B-OM had a history of hypertension, while 4 patients (28%) were hypertensive in NB-OM. Osteoporosis was observed in (5.8%) of patients with B-OM and in one patient (7.1%) of patients with NB-OM (without antiresorptive treatment). Six patients (11.5%) with B-OM suffered from malignant underlying disease, without been treated with radiation, bisphosphonate or denosumab, whereas no cases of such diseases were reported in patients with NB-OM (Table 2).

With regard to the relevant medications, 4 patients (7.7%) with B-OM and 2 patients (14.3%) with NB-OM had a history of steroid intake. Three patients from the bacterial type (5.8%) were treated with immunosuppressives and no record of immunosuppressive treatment in NB-OM patients was observed (Table 2).

4.5 Risk factors

The most common preceding event to B-OM was dentoalveolar surgery (42.3%), while it was tooth extraction for NB-OM (33.3%) (Table 2). Mandibular fracture was also identified as a risk factor for the development of B-OM (17.3%). The most frequent behavioural risk factor associated with OM was smoking (B-OM: 18 patients, 34.6%; NB-OM: 4 patients, 30.8%), followed by alcohol abuse (B-OM: 13 patients, 25%). When comparing the two types of OM, the difference between smoking habits in B-OM and NB-OM was statistically insignificant between the two groups. However, for heavy alcohol consumption, the B-OM group showed a statistically significantly higher prevalence than the NB-OM group (Table 2).

4.6 Clinical presentation

An overview of the signs and symptoms for both types of OM reported pain as the most frequent symptom in 92.3% of cases with B-OM and in all cases of NB-OM, while the most common clinical finding was swelling, observed in 84.6% of patients with B-OM and 80.0% of patients with NB-OM. Inflammation was also a common
symptom in B-OM. Intra-oral fistulas were only apparent in B-OM in 26.9% of the cases. The majority of wound healing disturbances was recorded in 28.8% of B-OM group and in only 6.7% of the NB-OM group (Table 2).
Table 2: Descriptive statistics and results of comorbidities, triggering factors and treatment in the two groups of osteomyelitis

<table>
<thead>
<tr>
<th></th>
<th>Bacterial (n = 52)</th>
<th>Non-Bacterial (n = 15)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>5(9.6)</td>
<td>1(6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3(5.8)</td>
<td>1(6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15(28.8)</td>
<td>4(26.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Malignant underlying disease</td>
<td>6(11.5)</td>
<td>0(0.0)</td>
<td>0.325</td>
</tr>
<tr>
<td>Smoking</td>
<td>18(34.6)</td>
<td>4(26.7)</td>
<td>0.757</td>
</tr>
<tr>
<td>Alcohol</td>
<td>13(25.0)</td>
<td>0(0.0)</td>
<td>0.301*</td>
</tr>
<tr>
<td>Steroids</td>
<td>4(7.7)</td>
<td>2(13.3)</td>
<td>0.609</td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>3(5.8)</td>
<td>0(0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Preceding events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tooth extraction</td>
<td>8(15.4)</td>
<td>5(33.3)</td>
<td>0.146</td>
</tr>
<tr>
<td>Impacted wisdom tooth</td>
<td>1(1.9)</td>
<td>0(0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>DA-surgery</td>
<td>22(42.3)</td>
<td>4(26.7)</td>
<td>0.273</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>6(11.5)</td>
<td>2(13.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Fracture**</td>
<td>9(17.3)</td>
<td>0(0.0)</td>
<td>0.191</td>
</tr>
<tr>
<td>Unknown</td>
<td>6(11.5)</td>
<td>3(20.0)</td>
<td>0.407</td>
</tr>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>48(92.3)</td>
<td>15(100.0)</td>
<td>0.568</td>
</tr>
<tr>
<td>Wound healing disturbance</td>
<td>15(28.8)</td>
<td>1(6.7)</td>
<td>0.095</td>
</tr>
<tr>
<td>Swelling</td>
<td>44(84.6)</td>
<td>12(80.0)</td>
<td>0.699</td>
</tr>
<tr>
<td>Extra-oral fistula</td>
<td>12(23.1)</td>
<td>0(0.0)</td>
<td>0.055</td>
</tr>
<tr>
<td>Intra-oral fistula</td>
<td>14(26.9)</td>
<td>0(0.0)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Sensibility disorder</td>
<td>4(7.7)</td>
<td>1(6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Exposed bone</td>
<td>3(5.8)</td>
<td>0(0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>5(9.6)</td>
<td>0(0.0)</td>
<td>0.580</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>2(3.8)</td>
<td>15(100.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Surgical</td>
<td>50(96.2)</td>
<td>2(13.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Treatment modalities of B-OM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>51(98.1)</td>
<td>8(53.3)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Irrigation</td>
<td>10(19.2)</td>
<td>1(6.7)</td>
<td>0.433</td>
</tr>
<tr>
<td>PDT</td>
<td>6(11.5)</td>
<td>0(0.0)</td>
<td>0.325</td>
</tr>
<tr>
<td>HBOT</td>
<td>1(1.9)</td>
<td>1(6.7)</td>
<td>0.400</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>0(0.0)</td>
<td>9(60.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>I&amp;D</td>
<td>16(30.8)</td>
<td>3(20.0)</td>
<td>0.527</td>
</tr>
<tr>
<td>Curettage</td>
<td>10(19.2)</td>
<td>0(0.0)</td>
<td>0.101</td>
</tr>
<tr>
<td>Sequestrectomy</td>
<td>25(48.1)</td>
<td>0(0.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Debridement</td>
<td>13(25.0)</td>
<td>0(0.0)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Decortication</td>
<td>13(25.0)</td>
<td>2(13.3)</td>
<td>0.490</td>
</tr>
<tr>
<td>Local application of AB</td>
<td>4(7.7)</td>
<td>0(0.0)</td>
<td>0.568</td>
</tr>
<tr>
<td>Extraction of causative teeth</td>
<td>13(25.0)</td>
<td>1(6.7)</td>
<td>0.164</td>
</tr>
<tr>
<td>Continuity resection</td>
<td>1(1.9)</td>
<td>0(0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Plastic reconstruction</td>
<td>2(3.8)</td>
<td>0(0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Fracture treatment &amp; prevention:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction &amp; osteosynthesis</td>
<td>1(1.9)</td>
<td>0(0.0)</td>
<td>0.014*</td>
</tr>
<tr>
<td>Re-osteosynthesis</td>
<td>5(9.6)</td>
<td>0(0.0)</td>
<td>0.580</td>
</tr>
<tr>
<td>Protection plates</td>
<td>2(3.8)</td>
<td>0(0.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*: significant at P ≤ 0.05

**: Only 9 from the 14 fracture-treated case were triggered by the fracture itself, the other 5 cases were submitted under other proceeding events as the fracture was not the direct trigger.
**Results**

***: Fracture treatment & prevention include not only the cases admitted to our clinic with fractures leading to OM but also the cases with inadequate treated fractures or unsuccessful inserted osteosynthesis needing re-osteosynthesis and cases with weakness or defect in jaw needing fracture prevention using protection plates.

### 1.1 Radiographic features

Radiographic examination revealed the presence of irregular radiolucency and resorption of surrounding bone (sequester formation) in cases of fracture bone destruction and necrosis adjacent to the fracture site in B-OM, while NB-OM showed multiple radiolucent and radiopaque mass in the affected area of the mandible and appeared to be unattached to the root apices.

![Clinical and radiographic presentation of bacterial (B-OM) and DSO of the jaw.](image)

**Figure 5:** Clinical and radiographic presentation of bacterial (B-OM) and DSO of the jaw.

**Panel (A) B-OM:** Patient presented with extra-oral swelling of the left side of the face, trismus, signs of inflammation, fistula formation, pus discharge, palpable lymphadenopathy and scar formation. The lesion was related to the mandible with exposed necrotic bone involving the mylohyoid ridge intra-orally. Panoramic radiograph showed osteolytic changes observed at the fracture site related to the body of
the mandible. **Panel (B) NB-OM (DSO):** Patient presented with facial asymmetry and indurated hard swelling in the right side of the face without suppuration and cervical lymphadenopathy extra-orally. Intra-orally, the patient had normal intact mucosa without any lesions. Panoramic radiograph showed diffuse radiopaque and radiolucent alveolar bone changes in the body of the mandible related to the right molar region.

### 1.2 Treatment

When comparing management performed for both B-OM and NB-OM, surgical procedures were frequently used in the treatment of the B-OM group (50 cases; 96.2%); this was significantly higher than for the NB-OM group (4 cases; 26.7%). The main surgical procedures included incision and drainage, sequestrectomy and surgical removal of necrotic bone. In particular, sequestrectomy was frequently performed in the B-OM (25 cases; 48.1%). Furthermore, systemic antibiotic usage was significantly higher in B-OM (51 cases; 98.1%) compared to NB-OM (8 cases; 53.3%), the latter being mainly a diagnostic measurement in order to rule out B-OM. The bisphosphonate intake between the two groups was statistically significant. In NB-OM, bisphosphonate was administrated for 9 cases out of 15 (60%), whereas it was not used at all in the B-OM (Table 2).
Supplementary Table 1: Classification and clinical picture of OM

<table>
<thead>
<tr>
<th></th>
<th>Bacterial osteomyelitis</th>
<th>Non-bacterial osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical findings</strong></td>
<td>pain &amp; swelling</td>
<td>pain &amp; swelling</td>
</tr>
<tr>
<td></td>
<td>abscess formation and suppuration</td>
<td>no abscess formation, no suppuration</td>
</tr>
<tr>
<td><strong>Radiographic features</strong></td>
<td>osteolytic pattern</td>
<td>mixed pattern</td>
</tr>
<tr>
<td></td>
<td>formation of sequester</td>
<td>resorption and/or enlargement of external bone</td>
</tr>
<tr>
<td><strong>Histologic findings</strong></td>
<td>necrotic changes and inflammation of bone</td>
<td>inflammation changes of bone</td>
</tr>
<tr>
<td></td>
<td>Formation of abscesses and sequester</td>
<td>reactive hyperplasia of bone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>similarity changes to fibrous dysplasia</td>
</tr>
<tr>
<td><strong>Medication</strong></td>
<td>antibiotic</td>
<td>anti-inflammatory drugs such as corticosteroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&amp; bisphosphonate</td>
</tr>
</tbody>
</table>
2. Discussion

The purpose of the study was to draw on our experience with osteomyelitis to differentiate non-infectious osteomyelitis of the jaw as non-bacterial osteomyelitis from the bacterial type, highlighting some of the most important features in addition to the management of both types of OM.

Osteomyelitis is frequent in the facial area and its characteristics include malfunction, progressive inflammatory destruction, marked bone absorption in the affected area and atypical bone remodelling. The disease may lead to complications after orthopaedic and maxillofacial surgeries or small surgical interventions like teeth extractions (Fliefel et al., 2016). There are multiple reasons for osteomyelitis such as medications, radiation, odontogenic sources, trauma and in some cases, the cause remains unknown (Hong et al., 2016).

The disease is classified as acute until one month of clinical duration and chronic when it lasts longer (Hudson, 1993). Authors have classified chronic osteomyelitis into suppurative or non-suppurative recurrent multifocal and sclerosing, differentiating between the three classifications of acute osteomyelitis, contiguous focus, haematogenous type and progressive type (Miloro, Ghali, Larsen, & Waite, 2004).

Currently, more common osteomyelitis variants are regarded as chronic non-suppurative osteomyelitis of the mandible, referred to as primary chronic osteomyelitis (PCO), diffuse sclerosing osteomyelitis (DSO) and juvenile mandibular chronic osteomyelitis (JMCO) in the oral and maxillofacial surgical literature. Variable terminology has caused confusion and hampered understanding of the disease process (Renapurkar, Pasternack, Nielsen, & Kaban, 2016).

Similar to previous studies, the most common symptom in B-OM was local pain, as reported in 94% of the cases (Catalano-Pons et al., 2008; Gikas et al., 2009; A. Jansson et al., 2007; Spindler, Huenges, & Hoppe, 1998). Other common findings, such as swelling, fistula, sequestrations and inflammation, also correlated with earlier studies for OM of the jaw (Prasad, Prasad, Mouli, & Agarwal, 2007). Fistula was present in more than one third of the patients, similar to that reported in other studies (Baur et al.,
Clinical signs of inflammation due to the increased blood flow to the inflamed area were noted, especially in the bacterial group as described previously (Dietz, Bachmeyr, & Joppich, 2004; Spindler et al., 1998; Voit, 2013).

In the study of Baur et al. (Baur et al., 2015), anaesthesia of the lower lip because of the affected inferior alveolar nerve was evident in 29.1% of patients. In the present study, this finding was evident in only 7.5% of all patients. This difference is accredited to the fact that the cases in our study were acute and chronic OM, compared with only chronic cases in Baur’s study.

With regard to the present study’s demographic findings, the majority of patients were female in both B-OM and NB-OM. This was in accordance with a review of 260 cases which found that females are four times more affected than males in NB-OM (Beretta-Piccoli et al., 2000). The median age of NB-OM was 9 years as reported in many studies (Job-Deslandre, Krebs, & Kahan, 2001; Jurik & Egund, 1997; Monsour & Dalton, 2010). When comparing the age prevalence between B-OM and NB-OM of patients, B-OM had a wider range of age compared to NB-OM. It presented in all age groups, which correlates with several previous studies and may be related to the systemic comorbidities and dental complications (Baur et al., 2015; Bevin, Inwards, & Keller, 2008; L. Chen et al., 2013; Tanaka & Hayashi, 2008). The onset of NB-OM was recorded in this present study, like in several others, mostly in adolescents and young adults (Bjorksten, Gustavson, Eriksson, Lindholm, & Nordstrom, 1978; Schilling, 1998; Schilling, Eckardt, & Kessler, 2000; Schilling & Kessler, 2001; Seidl, Maier, Refior, & Veihelmann, 2003; Sundaram, McDonald, Engel, Rotman, & Siegfried, 1996; Uhl M, 1995). Primary chronic osteomyelitis has been reported in children of both sexes, with a peak onset between 10 and 20 years (Gentry, 1988).

In the majority of the patients in our case series, the lesions were located in the mandible, with pain and swelling the most reported clinical findings, while the maxilla was rarely affected by OM due to the good blood supply of the maxilla and its unique spongy feature (Adekeye & Cornah, 1985). This is in agreement with numerous other studies (Adekeye & Cornah, 1985; Chronopoulos et al., 2015; Fliefel, Trolltzsch, Kuhnisch, Ehrenfeld, & Otto, 2015; Palla, Burian, Klecker, Fliefel, & Otto, 2016; Prasad et al., 2007; Taher, 1993). Even though fractures and trauma are important
predisposing factors of the disease, they rarely lead to osteomyelitis in the maxilla because of its excellent blood supply (Adekeye & Cornah, 1985).

With all the recent antimicrobial antibiotic drugs, the propagation of OM has been diminished, except in medically compromised patients. Nevertheless, risk factors and systemic conditions play a role in OM, thus have to be well studied and managed when treating OM as they may alter the bone's vascularity or modify the patient’s defence, thereby affecting the healing process (Pincus, Armstrong, & Thaller, 2009). The most prominent comorbidities identified in this study were hypertension (28.4%) and diabetes (9%), which was in line with other reports (Baur et al., 2015). Tobacco and alcohol use has been shown to be associated with this disease, with no significant difference between the two disease entities. However, alcohol consumption was significantly more prevalent in B-OM compared to NB-OM. This is in accordance with previous studies which implicated these habits as predisposing factors for B-OM of the jaw (Koorbusch et al., 1992).

The results of this study support the findings of another study of 88 cases of osteomyelitis of the mandible, which reported trauma as the most frequent trigger inducing the disease (Taher, 1993). In this study, dentoalveolar surgery was the most common preceding event of OM, followed by fracture. However, it needs to be emphasised that dentoalveolar surgery are usually caused by an infection (e.g. odontogenic infection leading to dental extraction). This differed from the findings of the Koorbusch study, which reported traumatic causes (36.1%), odontogenic infections (36.1%) and radiation and neoplasm (16.7%) (Koorbusch et al., 1992). Other studies revealed odontogenic infection to be the most predominant cause of the disease of a Nigerian population and that trauma-related causes had a much lower frequency (Akinmoladun et al., 2013). In contrast, some studies reported that traumatic and odontogenic causes have the same prevalence (36.1%) (Daramola & Ajagbe, 1982).

There is a wide range of treatment protocols for OM due to its complex nature (Fliefel et al., 2016). The treatment was differentiated according to the aetiology of the disease. Almost all cases (98.1%) of the B-OM were treated with antibiotics, in accordance with previous studies (Darville & Jacobs, 2004; A. F. Jansson et al., 2009; Karmazyn, 2010; Steer & Carapetis, 2004) and in line with recommendations in the

Chronic bacterial osteomyelitis also requires surgical intervention to create appropriate healing conditions, through the removal of the necrotic bone parts to acquire good, vital and vascularised surrounding tissue and through sequestrectomy and removal of soft and hard necrotic tissues (Lew & Waldvogel, 2004; Rao et al., 2011). In total, 96.2% of the patients included in this study had undergone removal of necrotic bone parts, whereas resection of jaw continuity took place in only 1.5% of patients. However, other studies on OM showed the use of antimicrobial therapy as a conservative treatment (Koorbusch et al. (1992).

Antibiotic therapy should start early during the treatment and continue post-operatively to prevent post-surgical infections (Nezafati et al., 2009). Antibiotics can be changed according to the antibiogram (Voit, 2013). However, record audits did not show a pattern consistent with culture-guided antibiotic therapy, as they were administrated only in cases were empirical antibiotics were found to be clinically ineffective. The treatment of NB-OM remains controversial (Eleftheriou et al., 2010), although the treatment of OM has been excessively developed in the past few years due to new antibiotics and anti-inflammatory drugs, non-bacterial osteomyelitis of the mandible does not always respond to medical treatment (Hino et al., 2005).

Some studies suggested glucocorticroid therapy in cases showing no-recovery after being treated with NSAIDS (Girschick et al., 1999; Girschick et al., 2005). Furthermore, alpha-interferon has been successful for the treatment of OM in some studies, but currently is not an accepted alternative for glucocorticoids (Andersson, 1995; Otsuka, Hamakawa, Kayahara, & Tanioka, 1999).

Despite the association between bisphosphonate intake and the occurrence of osteonecrosis reported repeatedly in the literature (Ärzteschaft, 2005; Carter & Goss, 2003; Hoefert S, 2004; Migliorati, 2003; Otto et al., 2012; Schwartz, 2004), several studies recommend bisphosphonate for the treatment of NB-OM and in particular, for CRMO.
Discussion

Other treatments reported in the literature include azithromycin, interferon, sulfasalazin, azathioprin, methotrexat, intravenous immoblubine or colchicin (Beck et al., 2010; Catalano-Pons et al., 2008; El-Shanti & Ferguson, 2007; Gikas et al., 2009; Huber et al., 2002; A. G. Jansson et al., 2002; A. G. Jansson et al. 2004; Schilling et al., 2000; Wipff, Adamsbaum, Kahan, & Job-Deslandre, 2011).

In this study, bisphosphonate and NSAIDs were the most commonly used drugs for the treatment of NB-OM based on the consensus recommendation of the German Society for Pediatric and Adolescent Rheumatology (GKJR) (A. Jansson, Jansson, & von Liebe, 2009; Wipff et al., 2011). Bisphosphonate was applied as an alternative therapy in NB-OM patients who did not respond to the treatment with NSAIDs (Otto et al., 2015; Seidl et al., 2003; Simm, Allen, & Zacharin, 2008). Consequently, 60% of the patients suffering from NB-OM were treated with an intravenous single shots of ibandronate as described by Otto et al. (Otto et al., 2015).

The most common surgical interventions in the present study were sequestrectomy, extraction of the causative teeth and debridement of the necrotic bone. Other surgical interventions such as curettage and partial resection did not show any long-term success (A. G. Jansson et al. 2004; Voit, 2013) but were added occasionally when needed to the treatment.

Even though antibiotic therapy did not have any effect on the progress of NB-OM in many studies (A. Jansson et al., 2002; Schilling, 1998; van Merkesteyn et al., 1990), 53 % of patients were treated before being referred to our hospital or during our diagnostic phase with antibiotics. This helped in the differential diagnosis, mainly to exclude the bacterial type of OM; after NB-OM was diagnosed, antibiotics were stopped immediately.

The typical clinical presentation of B-OM is pain, erythema and oedema of the affected part. This was different from NB-OM, where no existence of pus nor sinus tract were found (Lee, Sadigh, Mankad, Kapse, & Rajeswaran, 2016). Even though microbiological causes can be the initial preceding event, there are not enough studies to support a bacterial cause of the disease.
It has been reported that microbiological cultures are frequently sterile, and when bacterial contamination is detected, it was due to contamination of the sample by oral or skin flora according to whether the biopsy was transoral or extra-oral (Otto et al., 2015). Therefore, we suggest that the disease is named DSO, a metabolic bone disorder, rather than an infection.

2.1 Limitations of the study

The present study has several limitations. The study was retrospective, so some data may be missing. However, the study included much clinical information and patient data collected over a long period of time, and considered both types of OM. The study was conducted at a single-centre, multicentre studies would be useful to confirm the findings and to compare the data and management protocols. It is possible that the lack of a follow-up period may have affected the conclusion regarding disease management. Therefore, more studies are recommended, with a follow-up period applying the same treatment methods and further investigation of underlying diseases and their association with the incidence and prognosis of OM in both two types.
3. Conclusion

Most cases of osteomyelitis in this study were of the bacterial type. The disease was predominantly located in the mandible, with pain, swelling and inflammation the most commonly reported symptoms in a patient suffering from osteomyelitis. The majority of cases were preceded by trauma such as dentoalveolar surgery and fractures, followed by odontogenic infections, in particular when associated with unhealthy personal habits, such as smoking tobacco and high alcohol consumption. Bacterial osteomyelitis (B-OM) is a true infection originating from a wide range of microorganisms affecting the oral structures and is initiated by triggering factors. However, non-bacterial osteomyelitis (NB-OM) or diffuse sclerosing osteomyelitis (DSO), which is another different entity of chronic bone disorders potentially characterised by dysregulation of coupling between bone formation and resorption. Thus, using the terminology of osteomyelitis might be a misleading, contributing to the confusion in understanding the pathogenesis of the disease. Further studies are needed to exclude the role of bacteria in the disease. Finally, the convenient management of systemic diseases and awareness of the risks of smoking and alcohol consumption can reduce the occurrence of osteomyelitis of the jaw.
Summary

Bacterial osteomyelitis versus diffuse sclerosing osteomyelitis of the jaw, similar nomenclature, different disease entity

Introduction: Osteomyelitis (OM) of the jaw is considered one of the most challenging problems for dental clinicians. Many classifications of OM have been developed based on several characteristics including the clinical progression and pathogenesis of the disease. A particularly informative classification discriminates between bacterial osteomyelitis (B-OM) and non-bacterial osteomyelitis (NB-OM), presenting as diffuse sclerosing osteomyelitis (DSO).

Aim: To draw on our experience and observations of osteomyelitis of the jaw to differentiate between B-OM and NB-OM with respect to clinical, radiographic and microbiological findings, as well as discussing the treatment strategies of each type of OM.

Methods: The medical records of 175 patients were screened retrospectively, of which, a total of 67 patients were diagnosed with OM and treated surgically or conservatively at a single institution between January 2003 to December 2012. Demographic-, anamnesis-, clinical-, and radiological data were collected and evaluated. The patients were allocated into two groups depending on their aetiology, clinical and radiological features. Patients with history of radiation and bisphosphonate intake prior to OM diagnosis were excluded.

Results: The mean age of patients diagnosed with OM was 52 years and the mandible was the most commonly affected site. Moreover, behavioural risk, such as smoking and alcohol abuse, were commonly associated with OM. Notably, surgical procedures were significantly more frequent in the treatment of the B-OM group (50 cases; 96.2%) than in the treatment of the NB-OM group (4 cases; 26.7%).

Conclusion: Diffuse sclerosing osteomyelitis is distinct to other forms of osteomyelitis and the use of misleading terminology to describe DSO leads to confusion and misunderstanding of this disease.
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References


# Appendix

## ERFASSUNGSBOGEN

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<td>regelmäßiger alkoholkonsum:</td>
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Maligne Grunderkrankungen:
- ggf. Metastasen:
- ggf. Chemotherapie:
- ggf. Bestrahlung:
- ggf. Bisphosphonat:

Andere Erkrankungen:
Medikamente:
Steroide:

Immunsuppressiva medikamente:

Andere Medikamente:

Typ der Osteomyelitis:
Ggf. (ED)

Lokalisation der Osteomyelitis:
- Oberkiefer (OK):
- Unterkiefer (UK):

Klinischen Zeichen:
- Schmerzen
- Wundheilungsstörung
- Schwellung
- Entzündung
- Zufallsbefund
- Extraorale Fistel
- Intraorale Fistel
Therapeutischen Maßnahmen:

Konservative Therapie:
- Antibiotikatherapie
- Spül/Saugdrainagen
- Lokale Wundpflege (*ggf.* Photodynamische Therapie)
- Hyperbare Sauerstofftherapie
- Bisphosphonate applikation

Operative Therapie:
- Inzision & Drainage
- Kürettage
- Sequestrektomie
- Debridement nekrotischer Knochenanteile
- Dekortikation
- Evtl. topische Applikation von Antibiotika
- Extraktion verursachender (avitaler) Zähne
- Schienung beweglicher, jedoch vitaler Zähne
- Entfernung nekrotischer Knochenanteile und Knochenanfrischung bis zum vitalen Knochengewebe
- Partielle oder Kontinuitatsresektion
- Plastische Rekonstruktion
- Frakturstabilisierung
Mögliche auslösende Faktoren der Osteomyelitis

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Pathohistologisches Ergebnis:
(ggf. Einlage)

Mikrobiologischer Befund:
(ggf. Einlage)

Salah Mahaini
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Salah Mahaini
Munich 2018
Affidavit

Mahaini, Mohamad Salah Aldin

I hereby declare, that the submitted thesis entitled

**Bacterial Osteomyelitis versus Diffuse Sclerosing Osteomyelitis of the jaw, similar nomenclature, different disease entity**

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted, or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

---

Munich, 24.07.2018

Place, date

Mahaini, Mohamad Salah Aldin

Signature doctoral candidate
Confirmation of congruency between printed and electronic version of the doctoral thesis

Mahaini, Mohamad Salah Aldin

I hereby declare that the electronic version of the submitted thesis, entitled

Bacterial Osteomyelitis versus Diffuse Sclerosing Osteomyelitis of the jaw, similar nomenclature, different disease entity

is congruent with the printed version both in content and format.

Munich, 24.07.2018

Place, date

Signature doctoral candidate