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Diagnosis and Treatment of Osteomyelitis of the Jaw – A Systematic Review (2002-2015) of the Literature

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Corresponding author:** Gudmundsson T, Department of Oral and Maxillofacial Surgery, Odense University Hospital, Denmark, Europe**Received:** June 05, 2017; **Accepted:** June 23, 2017;**Published:** June 30, 2017**Abstract*Background and Aim:** To review the contemporary literature on the various types of osteomyelitis of the jaw and list treatment options, diagnostic measures, opinions and speculations concerning OM of the jaws.**Methods:** A Medline (PubMed) search was conducted and articles from 2002 and onwards was chosen.**Conclusion:** The current understanding of the predisposing factors and developmental phases of osteomyelitis of the jaw is insufficient. A widely diagnostic consensus is needed if reported data are to be used in meta-analyses.**Keywords:** Bone, diagnosis; Imaging, Infection; Jaw; Maxillofacial; Osteomyelitis; Therapy**Introduction**

Osteomyelitis (OM) is an inflammatory process of the bone. In the maxillofacial skeleton, usually both medullary and cortical bone are involved, hence the term is most often used to describe the inflammatory process in the basal and alveolar bone [1]. The most commonly used definitions of OM are an inflammatory reaction within the bone caused by bacterial invasion [2,3] or merely an inflammatory process of the bone, [4] both cortical and cancellous [5,6]. In the mandible, the most common sites are the body, followed by the symphysis, angle, ascending ramus and condyle [7]. OM is very rarely seen in the maxilla [6].

OM of the jaw can be a difficult disease to treat because the chronic forms have a marked tendency towards recurrence. OM of the jaw is not a singular entity. In the literature, two main types of OM are described. The presence of pus and/or fistulas and/or sequestrations are characteristics of the suppurative variants, thereby distinguishing them from the non-suppurative variants, which are chronic inflammatory processes of unknown etiology [5,6,8]. Even though OM of the jaw is a relatively rare condition, there are numerous differential diagnoses and classifications. Unfortunately, there is a lack of international consensus about their respective definitions, which makes it difficult to analyze and evaluate the reported data. Likewise, there are counter reports of differing treatment plans and find great variation in diagnostic approaches and follow-up regimens. This lack of diagnostic agreement and different approaches to treatment reflects the inadequate understanding of the predisposing factors and processes leading to OM of the jaw.

In the first main type of OM, infectious pathogens can be identified, appearing at different stages in pus, abscess/fistula and sequestration [1]. In the vast majority of these cases, there is an apparent odontogenic, infectious etiology [6] or some level of trauma introducing pathogens into the tissues [5]. This is defined as Secondary Chronic Osteomyelitis (SCO) [5,6,9].

Several authors define this type of OM of the jaw as a condition

of inflammation in bone marrow and cortex, with a pathogenesis directly associated with pathogenic microorganisms [1,3,10,11]. Accordingly, this type of OM should be seen only in association with infected foci, or where pathogens have been introduced through the mucous membranes or bony tissue have been exposed. Blood-borne pathogens are also capable of initiating OM of the jaw, which is mostly seen in pediatric patients and in immuno compromised patients [12].

The other main type of OM is a non-suppurative chronic variant with an insidious unexplainable onset, occasionally without culturable/detectable pathogens [6]. This is defined as a chronic inflammatory disorder of the cortical and cancellous bone of unknown etiology [5,8,13,14] or simply as chronic non-suppurative OM [1,6,9]. Characteristic of this type of OM is the lack of an acute state and the development of symptoms over the course of a few days to weeks. There may be periods without symptoms followed by exacerbations [5,8,13]. This definition applies to Primary Chronic OM (PCO) [5,6,9,14], Diffuse Sclerosing OM (DSO) [4], Diffuse Sclerosing OM of the Mandible (DSOM) [4], Juvenile Mandibular Chronic OM (JMCO) [8], Chronic Recurrent Multifocal OM (CRMO) [13], and chronic nonbacterial OM (CNO) [15] In this review these diagnoses are categorized as non-suppurative OM. (The term diffuse sclerotic OM is a broad radiologic description and also an excellent example of the confusing classification of OM. The diagnosis DSO has been reported in both bacterial and non-bacterial OM. Normally DSO is synonymous with PCO) [5,6].

Radiologic, clinical and histologic characteristics mentioned in this selection of articles suggest that these diagnoses describe nearly identical conditions or possibly identical conditions at different expressions or stages. Apparently, the main differentiating feature of CRMO from PCO, DSO, DSOM and CNO is the detection of more than one affected site. Other distinguishing histopathologic features have not yet been established [5,9]. Consequently, PCO, DSO and DSOM are by some considered as expressions of CRMO [4,9]. Eyrych et al. are not convinced as they detected microabscess formation (which is not previously reported in gnathic bone lesions

of CRMO and only once in DSO) and no extragnatic involvement in 10 of their 11 childhood and adolescence PCO patients, which seems to suggest a different disease process [5]. Theologie-Lygidakis reports similar finding in three of five juvenile PCO patients [14]. Furthermore, CRMO is considered an expression of the SAPHO syndrome (synovitis, acne, pustolosis, hyperostosis, and osteitis) [4-6,13]. Several authors agree on this, but according to Bevin et al. there is debate of whether SAPHO syndrome should be recognized at all, as there is less than 50% association of signs and symptoms [9].

PCO seems to have a stage-like course. Initially it is often seen with a radiographically mixed sclerotic and osteolytic pattern, which later on changes to sclerotic [5]. The sclerotic changes are characteristic of DSO.

The term non-suppurative does not exclude the presence of pathogens. It seems unclear whether non-suppurative OM of the jaw is aseptic or not, or if both possibilities exist. Krakowiak et al. describes chronic non-suppurative OM as caused by certain bacteria (*Actinomyces* and *Eikenella corrodens*) presenting mild or no symptoms and so often diagnosed several years into the disease process [7]. Other authors report negative bacterial findings indicating a non-bacterial pathogenesis [6,8,14].

Culturing or even detection of pathogens in cases of OM remains challenging. This may be caused by difficulties in biopsy handling and/or insufficient culturing techniques or it may, in some cases, actually be a result of absence of bacterial pathogens. These hypotheses are not easily validated. Some authors suspect results from biopsies are due to contamination in the trans-oral harvesting procedure [6]. Several scenarios of bias are feasible. It is thinkable that current culturing techniques are predominantly detecting contamination and not the causative pathogens. Maybe the dynamic nature of the flora masks the initiating pathogens as they are later on surpassed by other bacteria. Maybe a polymicrobial flora requires very specific culturing media. Maybe the detected bacteria in non-suppurative OM are due to secondary infection caused by previous surgery or biopsy. Maybe negative culturing is caused by inadequate techniques of biopsy specimen handling or laboratory culturing. Hence it is difficult to conclude if the cultured bacteria are the actual causative pathogens or if negative culturing means that chronic non-suppurative OM of the jaw is aseptic. Only few authors reported negative culturing of biopsies in mandibular OM [6,8,16]. Looking at articles by rheumatologists, aseptic OM of the extremities is acknowledged as a separate entity. CRMO is defined as aseptic [13].

Eyrich et al. suggest an overall OM categorization by defining primary chronic OM (PCO) as a chronic non-suppurative OM of unknown etiology, and secondary chronic OM (SCO) as a condition with suppuration, abscess/fistula formation, and sequestration at a later stage due to a defined, infectious etiology [5].

Another classification is based on duration of the symptoms. Acute OM (AO) and subacute OM are differentiated from Chronic OM (CO) by a time line of (usually) 1 month, meaning that OM is considered chronic if the duration exceeds 4 weeks/1 month [1,5,6,9,14]. Other authors consider OM as chronic when the duration exceeds 6 weeks [17]. This classification is to our knowledge used mainly for pyogenic OM.

OM of the jaw is very likely several multifactorial clinical entities presenting themselves with similar symptoms and radiologic appearances.

Materials and Methods

Selection of articles for this review was made from PubMed searches with the following key words: "Osteomyelitis AND jaw", "treatment, chronic osteomyelitis AND jaws AND diagnosis". The focus has been on the contemporary literature; consequently the search was limited to articles published in 2002 and onwards. The titles and abstracts were screened for relevancy. 23 articles were selected for this review. Specific PubMed and other searches in order to find additional material are mentioned in the text. The PRISMA statement was followed [18].

The original intent of this article was a systematic review of the contemporary articles from 2002 and onward. The aim was to categorize reported diagnostic and treatment modalities for the infectious and non-suppurative types of OM of the jaw and statistically evaluate the clinical outcomes in terms of success rates, failure rates and expected rates of recurrences. However, this turned out nearly impossible, as the lack of international diagnostic agreement and differing diagnostic measures were encountered. Due to the rarity of some forms of OM, articles are often presenting a very modest number of patients without control groups, making the level of evidence low. Consequently, it was decided to review the contemporary literature and list treatments, diagnostic measures, opinions and speculations concerning OM of the jaws.

Diagnosis

OM of the jaw has proved a challenging condition to effectively diagnose, treat, and cure. As previously mentioned, there are multiple diagnoses for different manifestations of OM of the jaw, some of which are sub classifications, other may be the same condition in a different stage or a different expression. Some diagnoses merely reflect the radiologic appearance, the number of affected foci, the age group of the patient, the presence or absence of pus or recurrent nature of the disease. Many different diagnostic techniques have been proven to be useful, but so far the agreement among many authors is that the final diagnosis should be based on the following parameters: (1) the clinical presentation and history of the patient, (2) imaging techniques, (3) culturing, and (4) histologic analysis [12,14].

Clinical presentation

Local intense pain, tenderness, fever, painful or painless swelling, purulent discharge, intraoral fistula, skin fistula, trismus, hypoesthesia of the inferior dental nerve, and pathologic fracture are among the common symptoms in suppurative OM. If the bacterial infection is less virulent, symptoms can mimic an acute or prolonged alveolar osteitis making diagnosis and selection of relevant treatment difficult [1].

Non-suppurative OM of the jaw, e.g. PCO, is characterized by recurrent pain, swelling, limited mouth opening, absence of suppuration [8,9], periostitis, occasionally regional lymphadenopathy and reduced inferior alveolar sensation [6].

Radiographic appearance

PCO in the mandible is typically seen with a mixed pattern

Table 1: Different OM diagnoses and classifications.

Chronic non-suppurative OM variants:	
Primary chronic OM (PCO)	Non-specific non-suppurative inflammatory process of unknown etiology, in general suspected aseptic.
Diffuse sclerosing OM (DSO)	Usually synonym for PCO, refers to radiologic appearance. Often referred to as mandibular expression of CRMO ⁷ .
Focal sclerosing OM (FCO)	
Chronic recurrent multifocal OM (CRMO)	CRMO is currently considered the most severe form of SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis) ⁷ .
(Recurrent) chronic non-bacterial OM (CNO)	
Unifocal chronic non-bacterial OM	
Non-recurrent chronic non-bacterial OM	
Non-suppurative OM	
Juvenile primary chronic OM (JPCO)	Suggested as a separate entity of PCO in children and adolescents.
Juvenile mandibular chronic OM	As JPCO, in the mandible.
Infectious OM variants:	
Acute OM (AO)	OM of infectious etiology, duration of symptoms less than 4-6 weeks.
Secondary chronic OM (SCO)	OM of infectious etiology, duration longer than 4-6 weeks. (May even be PCO with secondary infection).
Chronic suppurative OM	Pyogenic OM, duration longer than 4-6 weeks.
Traumatic mandibular OM	Infectious OM of the mandible, following mandibular trauma.
Recurrent chronic suppurative OM	Recurrent infectious OM
Chronic OM	Infectious, chronic OM ¹
Subacute OM	Asymptomatic OM
Non-specific OM diagnoses:	Diagnoses do not specify infectious or aseptic origin.
Localized OM	OM at a single location
Chronic refractory OM ¹	Only mentioned, not explained ¹

of sclerosis and osteolysis [5,14]. There may be widening of the mandible, periosteal bone reaction [8,13] and an unidentifiable cortical-medullary border [5,6]. In the later stages there seems to be a shift towards only sclerotic changes [5,6]. Lamination of periosteal new bone and sequestra are radiologically distinguishing features of OM [10]. PCO often show patchy osteosclerosis and osteolysis and frequently the “onion-skin appearance” of subperiosteal bone formation [9].

Imaging techniques

Conventional radiographs: These were the standard imaging technique for many years. Now, they are recommended for the initial screening and as adjunct in selecting and interpreting other imaging techniques [12]. Radiographs are readily available and yield a low exposure of radiation to the patient [7]. Sensitivity and specificity rates for plain films are reported to be 14% and 70%, respectively [12]. The accuracy of plain radiography is limited, especially after surgery in which, bony structures are destroyed [17]. The disease process may not be recognized on radiographs in its early stages [1,7,10,12]. Panoramic projections are useful in cases of maxillofacial OM [7].

CT scans: As a single modality, CT scans are considered useful in initial surgical treatment planning in cases with overt bony destruction [12] and as a mean of staging and following lesions [13]. The multiplanar slices and computer-generated 3D reconstructions are obviously easier to interpret than conventional radiographs, and the ability to create stereolithic models can be very helpful in planning the surgical treatment [7]. With the use of contrast medium,

medical-grade CT scans are capable of visualizing soft tissue changes [7]. Cone beam CT scans are capable of creating a three dimensional image of a focused area with a significantly lower radiation dose than conventional CT scans [13].

PET/CT scans: Positron Emission Tomography (PET) scans using fludeoxy glucose F18 have shown promising results in the diagnosis of OM of the jaws, especially when combined with traditional CT scans. These 2 modalities fuse the anatomic structures and a metabolic state, thereby obtaining a 3D image with high sensitivity and specificity. Individual PET scans have a much higher rate of false-negative and false-positive results [7]. As this is a relatively novel diagnostic approach, additional research is needed [7].

Laser Doppler flowmetry: Is mentioned by some authors [10,12]. This technique has shown that medullary inflammation leads to a decrease in mandibular blood flow [12], but there is no further description of indications, image values or techniques [10].

MRI scans: These scans used with gadolinium contrast agent show early OM changes [7] and are suitable in detecting early and acute OM [12]. MRI scans do not show specific features necessary for making a diagnosis, but reveal the extent of the lesions and can be helpful in disease monitoring [1,13] and are a safer alternative to the radiation dose of the CT scan [13]. MRI is less sensitive to inflammatory changes than CT and cone beam volumetric tomography because marrow changes may take months to normalize [13]. MRI has limited ability to discriminate between edema and infection and the presence of metal implants obscure image diagnostic value [12].

Table 2: Imaging techniques and their characteristics in OM.

Imaging technique	Sensitivity	Specificity	Recommended use	Radiation dose
Conventional radiographs	14%	70%	Initial support of clinical suspicion	Intraoral: <1,5 µSv Panoramic: 2,7-24,3 µSv
CT scan	NA	NA	Initial surgical treatment planning for patients with overt bone destruction	Multi slice CT, maxilla-mandibular: 280-1410 µSv Cone Beam CT Dentoalveolar: 11-674 µSv Cone Beam CT Craniofacial: 30-1073 µSv
MRI	60%	85%	Early pre-surgical diagnosis of chronic OM	None
¹¹¹ In scintigraphy	21% (axial skeleton)	NA	Un-useable as single modality for maxillofacial region	NA
⁹⁹ Tc + ⁶⁷ Ga scintigraphy	98%	NA		NA
Single photon emission CT (SPECT)	84%	Low	False-negative findings in tumor-patients with elevated blood glucose	NA
Fluorodeoxyglucose-positron-emission-tomography	64%	NA		NA

Nuclear scans: The most common scintigraphic agent is technetium 99m, which marks increased bone turnover. Other agents are indium 111 and gallium 67 [7]. Bone scintigraphy with Single Photon Emission Computed Tomography (SPECT) is reported to be superior in the initial treatment phase because of its high sensitivity (84%). In the follow-up period, Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) is more suitable because it has a better correlation with the course of the disease and remission [17]. Osteoblast activity results in an increased uptake of ^{99m}Tc-MDP, which leads to a false-positive scintigraphy reading for weeks or months after recovery or successful surgery, as a sign of bone remodeling [17]. Krakowiak et al. report 98% sensitivity when the scintigraphic agents ^{99m}Tc and ⁶⁷Ga are combined, as gallium is sensitive to inflammatory changes. This combination can show changes as early as 3 days after the onset of infection. But as scintigraphy exposes the patient to a radiopharmaceutical agent, its use should be limited to cases where a diagnostic benefit is expected [7]. Obel et al. recommend SPECT/low dose CT as an alternative to conventional CT scans, as X-ray exposure is reduced and images are improved with the fusion of functional and anatomic information [8]. Radioisotope bone scans can often identify other areas of involvement [10].

Immunologic workup: In acute OM, the leukocyte count is significantly increased, up to more than 15,000, in about one-third of patients. The erythrocyte sedimentation rate and C-reactive protein values may also be elevated [6,7]. Laboratory analysis of C-reactive protein and immunoglobulins IgA, IgM and IgG show a poor correlation with disease progression in patients with chronic OM of the mandible (with infection). IgG reaches the highest correlation, with a sensitivity of 46% and specificity of 75% (95% confidence interval). Correlations with the other parameters are poor [17].

Reports of elevated erythrocyte sedimentation rate and C-reactive protein values, with normal to slightly elevated lymphocyte counts are reported in some PCO cases [5]. Other authors report normal blood test results [14]. Eyrich et al. speculate that this may be due to samples taken at different stages of the disease [5].

Differential diagnostics

Bacterial OM of the jaw: Paget's disease, hypercementosis, fibrous dysplasia, early stage malignant bone tumors [10]. Radiographic differential diagnoses include osteogenic sarcoma and fibrous dysplasia [10].

Non-suppurative OM of the jaw: PCO has a resemblance to malignancies like osteosarcoma, chondrosarcoma, Ewing's sarcoma [6,8], non-Hodgkin's lymphoma, metastatic disease [9], histiocytosis X, leukaemia and neuroblastomas [13]. Benign conditions to consider are fibrous dysplasia, ossifying and non-ossifying fibroma [6,8], juvenile parotitis, chronic sialadenitis [8]. Paget's disease, cementoma and nonspecific chronic lymphadenitis [5,9].

Histologic analysis

Marx et al. describes the following: suppurative OM of the mandible shows necrosis of the bone as evidenced by empty osteolytic lacunae, absence of osteoblastic rimming, and empty Haversian canals. The number of inflammatory cells in the marrow space varies. These cells are a mixture of neutrophils, plasma cells, histiocytes, and lymphocytes. Active osteoclasts are seen in 96% of specimens. Despite the lack of blood vessels in the Haversian and Volkmann canals, capillaries and arterioles are noted in the marrow spaces. Ninety-one percent of the specimens show hyperemia or thrombosis in these marrow spaces. Surprisingly, microorganisms are only recognized in 33% of specimens. Microorganisms are difficult to demonstrate within bone which may be a result of the decalcification processing. Reactive viable bone at the surface is seen in 74% of specimens. The presence of reactive bone and a viable periosteum suggests that the disease mechanism initiates in the marrow space and stimulates the layering of periosteal bone. The histopathologic evidence in the suppurative OM specimens indicates an inflammatory response caused by toxins released from microorganisms, leading to blood vessel thrombosis, thereby creating an anaerobic environment. Twenty of 23 specimens cultured obligate or facultative anaerobic species [19].

Non-suppurative OM (PCO) is characterized by chronic non-specific inflammation, increased bone resorption and deposition of varying degrees [6]. Bone sclerosis and medullary fibrosis are also commonly seen [9]. Baltensperger et al. found no bacteria in 3 of 21 specimens. In one of these cases a Polymerase Chain Reaction (PCR) was performed but showed no sign of bacterial DNA/RNA [6]. Obel et al. also report negative bacterial culturing from a bone biopsy in a JMCO patient [8]. Theologie-Lygidakis did not identify any bacterial causative factor in three of five surgical specimens, cultured both aerobic and anaerobic [14]. Apparently, some cases seem to be aseptic.

Treatments

Treatment aims differ depending on whether or not bacterial infection is apparent, but surgery remains similar. In the septic

Table 3: Detected bacterial species in OM of the jaw.

Bacterial species in OM		Authors
<i>Streptococcus</i>	*Hematogenous seeding seen in patient with long-term catheters	Coviello and Stevens
<i>Bacteroides</i>		
<i>Lactobacillus</i>		
<i>Eubacterium</i>		
<i>Klebsiella</i>		
<i>Salmonella</i>		
<i>Pseudomonas sp*</i>		
<i>Serratiasp**</i>		
<i>S aureus**</i>		
<i>Staphylococcus epidermis**</i>		
<i>P aeruginosa**</i>		
"Mixed anaerobes", some		Patel, Harwood and McGurk
<i>Viridans streptococci</i>		
<i>Actinomycesnaeslandi</i>		
<i>Staphylococcus epidermis</i>		Bevin, Inwards and Keller
<i>Streptococcus viridans</i>		
<i>Acinetobacter calcoaceticus</i>		
<i>Veillonellaparvula</i>		
<i>Neisseria</i>		
<i>Haemophilus parainfluenza</i>		
<i>Staphylococcus sp</i>		
<i>Haemophilis influenza</i>		
'Mixed oral flora'		Lucchesi and Kwok
<i>Actinomycesisraelii</i>		Wimalawansa
<i>Streptococci</i>		Humber, Albilal and Rittenberg
<i>Actinomyces</i>		
<i>Eikenella</i>		
<i>Staphylococcus spp. (in 86,8%)</i>		Lukosiunas, Kubilius, Sabalys, Keizeris and Sakavicius
<i>(Staphylococcus aureus in 69,1%)</i>		
<i>Streptococci (in 42,0%)</i>		
Obligate or facultative anaerobic species in 20 out of 23 cases		Marx and Tursun
<i>Streptococci viridansspp (10/18)</i>		Baltensperger, Grätz, Bruder, Lebeda, Marek and Eyrich
<i>Staphylococci spp (8/18)</i>		
<i>Enterococci (2/18)</i>		
<i>Peptococci (2/18)</i>		
<i>Actinomyces (2/18)</i>		
<i>Propionibacterium (2/18)</i>		
<i>Neisseria (3/18)</i>		
<i>Veillonella (2/18)</i>		
<i>Haemophilus (3/18)</i>		
<i>Porphyromonas (1/18)</i>		
<i>Fusobacterium (1/18)</i>		
<i>Klebsiella (1/18)</i>		

Actinomyces spp	Eyrich, Baltensperger, Bruder and Graetz
Veillonellaspp	
Streptococcus viridans	
Actinomyces	
Propionebacteriumspp	
Haemophilusspp	
Staphylococcus spp	
Neisseria	
Corynebacterium	
Actinomyces	Krakowiak
Eikenellacorrodens	
'mixed oral flora from oral and panfacial sinuses and skin in trauma cases'	
Staphylococcus aureus	
Staphylococcus epidermis	
Prevotellaspp	
Candida infections	Kim and Jang
Streptococci	
Staphylococci	
Bacteroidesspp	

variants, infection control is the primary concern. Secondary to infection control, the treatment should facilitate reestablishment of sufficient blood supply. The theory of a compromised blood flow as a critical factor in the development of OM has been widely recognized [12], and the surgical procedures are performed with the aim of countering this. The common goal of all the surgical techniques is sufficient removal of necrotic and affected tissue while preserving peripheral viable bone in order to facilitate bone healing and/or future reconstruction of the defect(s) [14].

Surgical treatment: In the literature surgical treatment is widely recommended. Debridement of affected tissue, decortication with or without bone grafting, sequestrectomy, and saucerization, sometimes done repeatedly, are standard surgical procedures. Removal of involved teeth is advocated by some as retained teeth pose a risk of maintaining infection or present a pathway for bacteria [9] and are suspected as reason for treatment failures [10]. In some cases partial resection and simultaneous or staged reconstruction of the resected bone is performed. Resections with loss of continuity should only be used in severe cases. In the mandible, decortication seems to be the most widely preferred surgical procedure in both septic and the aseptic cases. Early intervention reduces the morbidity and extent of the surgery required [7]. The non-suppurative forms of OM (PCO, DSO, CRMO) are reported to show a poor response to surgical treatment [8] (also in combination with antibiotics, NSAIDs, and hyperbaric oxygen) [16].

Non-surgical treatment

Medications: The commonly used medications against OM of the jaws are antibiotics, NSAIDs, steroids and various chemotherapeutic agents. Apart from antibiotics and NSAIDs, these drugs are characterized by their role in modulating bone turnover and the immune system responses.

Antibiotics: Nearly all authors initiate treatment with antibiotics, often before the diagnosis of OM is established. Only few reports of antibiotics as a single treatment among our selection of articles, possibly because these would seem uninteresting or maybe the condition is cured in such early stage that the criteria of the diagnosis acute OM is not yet met. Once the diagnosis is established, the reported antibiotic regimens vary. In infectious OM, the dynamic nature of apolymicrobial flora [2,12] makes targeting the antibiotic difficult and the need for adjusting the antibiotic regimen during the course of the disease and according to culturing of specimens, is necessary [10]. Increasing bacterial resistance to antibiotics can negatively affect treatment outcome [12]. The recommended duration vary from 2 weeks to 6 weeks, typically beginning with intravenous antibiotics followed by a variable period of oral antibiotics. A protocol of surgical debridement and intravenous antibiotics for 1 week followed by oral penicillins for 3 weeks is also shown successful [20]. Kim et al. report 94,9% successful outcome when surgery is followed by 2 weeks of intravenous antibiotics (augmentin, cefazolin and an aminoglycoside) followed by 6 weeks of oral administration (augmentin and roxythromycin. Clindamycin and metronidazole were used according to culturing and sensitivity tests) [10]. Patel et al. recommends combined courses of IV and PO antibiotics (Ceftriaxone IV and Metronidazole PO for four weeks or Clindamycin IV for two weeks followed by co-amoxiclav for four weeks) as oral antibiotics alone seem ineffective in resolving the infection [1]. In the later stages of OM where necrotic bone is present, antibiotic diffusion throughout dead bone is compromised and without effect regardless of the external concentration [1]. In general antibiotics are considered an important part of the treatment of infectious OM of the jaws, but it is most commonly combined with other treatment modalities.

There seems to be agreement that antibiotic treatment alone has little or no benefit in PCO [8,14]. Postoperative antibiotic

administration in PCO is standard procedure for preventing infection, but again regimens vary. Theologie-Lygidakis et al. recommends amoxicillin/clavulanic acid combined with metronidazole for 2-3 weeks, or ciprofloxacin combined with clindamycin in penicillin-allergic patients [14].

New artificial antibiotics: Linezolid and tigecycline have shown very promising results against multidrug-resistant bacteria in the treatment of OM. In a study of 54 patients with orthopedic infections not limited to the jaw, treatment with linezolid, an oxazolidinone, yielded a 90% success rate [12]. Another retrospective review of linezolid efficacy showed an 84.8% cure rate in 66 patients suffering from chronic OM [12]. Both studies, however, reported a relative high rate of adverse effects that lead to cessation of treatment, 18% and 34.8% respectively. Subsequently the authors suggest, that linezolid should be reserved for the treatment of drug-resistant pathogens or when glycopeptide administration is not possible due to adverse effects, resistance, allergy or lack of intravenous access [12]. Unfortunately linezolid is still very expensive and at current time not standard treatment [12]. Tigecycline, a glycylcycline, is a derivative of tetracycline and active against multidrug-resistant gram-positive and gram-negative organisms and anaerobes. In a rabbit OM model with methicillin-resistant *S.Aureus*, tigecycline in combination with rifampin was 100% successful in clearing bone samples. Tigecycline and vancomycin alone were 90% successful. The most common adverse effects are nausea (43.2%), vomiting (26.7%), and diarrhea (12.7%) which led to a 6.2% discontinuation rate [12].

Local antibiotic delivery systems: Non-resorbable and resorbable: A Non-Resorbable polymethylmethacrylate (PMMA) bead can be used to elevate local drug levels. However, they require a second surgical procedure for removal, the local release of antibiotic is unpredictable, and low-grade foreign-body reactions are common [12].

Many different biodegradable materials have been tried: polylactic acid, polyglycolic acid, polyparadioxanone, polyesters, hydroxyapatite, bioceramics, polymer-ceramic composites, calcium phosphates, fibrin sealant implants, and collagen sponges. These have not been tested in OM in humans, but several animal studies show promising results [12]. The advantages over non-resorbable carriers are a predictable local release of antibiotics, and there is no requirement for a second surgery [12].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): The mechanisms of action of NSAIDs are not described in this selection of articles, hence a Google search with “NSAID” AND “mechanism” was performed. NSAIDs are well-known for their pain relieving and anti-inflammatory properties. NSAIDs act by inhibition of Cyclooxygenase (COX), an enzyme responsible for the formation of prostaglandins, prostacyclins, and leukotrienes. These cellular mediators participate in the regulation of diverse cellular processes, such as neovascularization, vascular homeostasis, development of fever and inflammation, and modulation of pain receptors [21].

Some authors report that NSAIDs are seemingly acting as a curative treatment of PCO, or at least beneficial as it reduces pain and swelling [8]. The exact mechanism of action in PCO is unknown. A Google search with the search words “NSAID angiogenesis” lead

to an article describing an animal study, where NSAIDs are shown to increase the number of stem and progenitor cells in circulating blood by four to six times [22]. A small human study (seven healthy volunteers) also showed increased cell mobilization [22]. This mechanism may be of importance. Future studies are needed to elucidate the role of NSAIDs in PCO and other OM variants.

Steroids: Systemic steroid treatment is used by some authors on PCO[8] There seems to be a relieving effect on symptoms [8]. The mechanisms of action are not described in this selection of articles.

Hyperbaric oxygen: HBO increase oxygen tension in the tissues, thereby countering the local effects of hypoxia in medullary infections [1] and aids hemangiogenesis and the reestablishment of blood flow in the tissues [2]. Increased oxygen tension enhance polymorpholeukocyte killing [1,8] fibroblastic and osteoclastic activity [2] and the formation of oxygen radicals is directly killing anaerobes and facultative anaerobes [2].

Handschel et al. reported that Hyperbaric Oxygen (HBO) was a successful treatment for chronic OM of the mandible in 27 patients receiving 40 “dives”. Success rate, measured by lack of clinical symptoms, as a single treatment was 54% (7 of 13 patients). As an adjunct, success rate was 75% (3 of 4 patients; with only one episode of relapse and previous antibiotic treatment) and 44% (4 of 9 patients; with several relapses, at least one surgical treatment and previous antibiotic treatment) [23]. Kim et al. recommends HBO in combination with antibiotics and surgery in refractory cases where previous antibiotic treatment and surgery have proved insufficient[10] Hakim et al. mention HBO as an adjunct in complicated cases such as osteoradionecrosis [17]. Krakowiak et al. emphasize the lack of large-scale human prospective data studies supporting the use of HBO in early or acute OM and considers HBO as an adjunct in refractory cases or cases with host system incompetence [7]. Coviello et al. state that very few studies of HBO related to wound healing are meeting quality criteria as control groups. Only two studies related to chronic OM met their inclusion criteria. One concluded that HBO had no effect on length of hospitalization, rate of wound repair, or recurrence of infection. The other study reported 34 of 38 patients remained free of recurrent OM for an average of 34 months [12].

Chemotherapeutics

Bisphosphonates: Bisphosphonates are pyrophosphate analogs capable of potently inhibiting osteoclastic bone resorption/remodeling [4]. Disodium clodronate [6], pamidronate, and especially alendronate are reported to be effective as pain relieving agents in diffuse sclerosing OM of the mandible [4,16]. The mechanism of pain relief is not known. Urade et al. observed that pain and swelling often occur when osteolysis progress, so inhibition of osteolysis may be contributing to pain relief [4]. In a case report of DSO not responding to previous treatment with antibiotics and curettage, infusion of a 10mg dose of alendronate diluted in 500 ml saline completely resolved the facial pain within 24 hours, and the patient was free of symptoms on clinical examination and diagnostic imaging at 1-year follow-up [16]. Furthermore, Urade et al. report similar findings in a recurrent DSOM case of 15 years duration where a single infusion of 45 mg pamidronate diluted in 500 mL saline solution gained complete pain resolution within three days [4]. The same authors did a review of the

previously reported cases of DSOM treated with bisphosphonates, which in 2012 was six articles, 4 of these case reports, the other 2 describing six and seven cases respectively [4]. These reports show remarkable result, but the number of cases is low and there is a lack of long term follow-up. The effect of bisphosphonates in treatment of infectious/pyogenic OM is only reported by Urade et al. However, their biopsy cultured negative on bacterial counts [4].

Methotrexate: A PubMed search reveals only one article mentioning methotrexate in treatment of OM (CRMO) involving the mandible. Paim et al. recommends methotrexate in painful and refractory cases, presenting three cases where one of the patients saw clinical improvement after two months of NSAID (rofecoxib 25 mg/day) and methotrexate 20 mg/week after non successful treatment with prolonged antibiotics, NSAID and antibiotics, then NSAID and 80 sessions of HBO, and prednisolone for one month [24]. Methotrexate is reported by Kaiser et al. in a retrospective study of 41 children with chronic nonbacterial OM, 33 multifocal, 4 unifocal and 4 SAPHO-syndrome. Seven of the patients received methotrexate and 6 had no obvious improvement. However, this article does not mention if any of the patients had involvement of the jaws [15]. Clearly, the role of methotrexate in treatment of non-suppurative OM of the jaws needs further documentation. Methotrexate should be used with caution as the side effects can be detrimental.

Calcitonin: Lucchesi et al. presented a case report on calcitonin as an adjunct to long term antibiotic treatment of chronic OM in the mandible. Calcitonin is a regulator of bone turnover, maintaining calcium balance and homeostasis. It inhibits prostaglandins and stimulates production of endorphins, thereby reducing bone pain and promoting healing. The authors believe that calcitonin played a significant role in the healing process, but stress that further clinical studies are necessary to clarify the true effect. In 2008 there was no previous documentation of calcitonin use in the treatment of chronic suppurative OM of the jaw [20].

Tumor Necrosis Factor alpha inhibitor: TNF-alpha inhibitor is mentioned in the review by Kaiser et al. as the drug with the highest percentage of clinical remission (46%) in 70 children with CNO (only one patient with mandibular lesion) [15]. A PubMed search for "osteomyelitis AND tumor necrosis factor" yields only 6 hits, most of these are case reports. Deutschmann et al. successfully treated a case of recurrent mandibular CRMO of ten years duration with TNF-alpha inhibitor infliximab [25]. Currently, the documentation of TNF-alpha inhibitor as a treatment of OM of the jaw is insufficient.

Discussion

Host factors

OM of the jaw has been associated with several systemic conditions like diabetes, [10] autoimmune deficiencies, rheumatic arthritis [10], cancer [10], chronic inflammatory bowel disease, Palmoplantar pustulosis, [13] syndromes, malignancies, malnutrition, alcoholism, AIDS, and sickle cell anemia [12]. Lukosiunas et al. found that 50 of 50 examined patients with traumatic OM caused by invading bacterial pathogens did in fact have some kind of immunologic disorder, e.g. cellular immunity dysfunction and reduced phagocytosis [11]. Kim and Jang found in their retrospective study that 14 out of 49 suppurative OM patients had documented systemic disease [10].

Theories of bacterial etiology

Introduction of bacterial pathogens into the bone initiates a local infection. The pathways may be through the mucosal barrier, through infected teeth or via the blood stream. These pathogens cause a chronic inflammatory process, which leads to a compromise of local blood flow and eventually leads to avascular necrosis. Local and systemic host factors may increase the patient susceptibility [1,7,12]. Many aspects of bacterial OM remain unanswered and obviously more future research is needed. It seems likely that a prolonged period of infection causes a change in the bacterial composition from initially aerobic towards anaerobic pathogens thereby possibly increasing treatment resistance.

Theories of immunologic etiology

A vascular deficiency (localized endarteritis) may cause the development of PCO [9] and chronic OM [1]. Speculations have been put forth that some bacterial pathogen(s) may trigger an immune response and that later on the process becomes independent of the pathogens [13]. Autoimmune disease is suspected to be responsible for triggering the PCO [9]. Bevin et al. suggest the possibility that PCO is initiated by an autoimmune process leading to endarteritis and vascular insufficiency. Their study indicates an association with diabetes mellitus because 2 of 4 cases had a strong family history of diabetes [9]. Monsour et al. present 3 theories of altered immune response: (1). a fragment from a micro-organism mimics a molecule in a bone or joint, the immune system then mistakenly attacks normal osteoarticular tissue; (2).- a fragment from the micro-organism couples with an immunoglobulin and is deposited in a bone or joint and activates sterile tissue; (3). a skin infection breaks down a barrier between immune cells and superficial skin tissues. The normal skin antigens are attacked by an immune cross-reaction that causes an inflammatory cascade. However, none of these theories completely explain the pathogenic process [13].

Biopsy and culturing

Bacterial OM: Cultures from bone lesion often show negative results and no specific microorganism has been identified as predominant [1]. There is no distinct bacterial pattern from positive cultures but the findings are often characterized as "normal oral or skin flora" [10]. which is why some authors consider these findings to be the results of contamination of the specimens [9].

Coviello and Stevens points out the following: that 93% of chronic OM cases are polymicrobial, with an average of 3.9 organisms per specimen, which obviously calls for a reliable method of culturing before commencing an appropriate antibiotic regimen. Proper handling of biopsy specimens is described as follows: "Specimens should be sent immediately to the lab as anaerobic species are lost in as little as 15 minutes and aerobes within 2 hours. Proper anaerobic handling takes into account ideal temperature (37°C) and differing carbon dioxide requirements" [12]. The challenge of culturing specific microorganisms is understandably complex and difficult to achieve in clinical situations. As a result, some authors question some of the reported biopsy bacterial findings because these might be due to contamination during the biopsy process or false negatives as a result of improper biopsy specimen handling or culturing [8]. There is no consensus on a defined biopsy and culturing procedure. Consequently, comparing and validating data seems unjustified.

An attempt to use blood samples instead of bone cultures proved that blood was a weak culturing media because concordance rates were only 30% between blood and bone samples in 100 OM patients [12]. Biopsy specimens are superior to swabs of purulent material as they yield higher bacterial counts. Yet another complicating feature is the fact that the bacterial composition has proved to be dynamic, meaning that in the later stages of the OM the initially prevailing pathogenic bacteria are suppressed or surpassed by other pathogens. This means that biopsy and culturing in order to adjust the antibiotic treatment as time progresses ought to be a routine procedure.

Aseptic OM

(CRMO, DSO and PCO): The triggering mechanism(s) of the inflammatory process are poorly understood. It is notable that several authors report that biopsies are negative regarding bacterial culturing [6,8,13], indicating a non-bacterial origin. (Some speculate whether this is actually the case and not just the result of false negative cultures, most likely caused by inadequate harvesting and culturing techniques). Other authors successfully cultured different bacteria, but as these are predominantly normal endogenous oral bacteria cultured from intraorally harvested biopsy specimens, they suspect the results are due to contamination [5,8]. There is also the possibility of secondary infection as many patients undergo several surgical procedures, including biopsies. This may turn a non-bacterial OM into a chronic septic OM, thereby obscuring diagnostics and complicating treatment. This speculation is not mentioned in any article in our selection, nor is there any standardized record of previous surgical interventions in patients with positively cultured specimens or biopsies.

Obel et al. describe 3 juvenile PCO patients successfully treated non-surgically using NSAIDs and steroids (antibiotics had seemingly limited effect) [8]. Paim LB. reports 3 juvenile cases treated with NSAIDs and steroids, one of them also receiving methotrexate [24]. Baltensperger et al. report an adult case with recurrent symptoms (previously received surgical treatment) treated similarly with success [6]. These cases certainly suggest a non-bacterial etiology, unless the biopsy results are considered false negatives (no reporting of biopsy after surgery by Baltensperger). Based on current findings it seems reasonable to assume that bacterial pathogens are not an etiologic factor in some cases of PCO, DSO and CRMO, but conclusive evidence is not available. If NSAIDs are in some cases curative, there must be some as yet unexplained key actions of the NSAIDs (triggering/boosting/modulating host immune response, perhaps by hemangiogenesis) on PCO. Whether NSAIDs may have a similar beneficial effect on bacterial OM of the jaw is not considered in this selection of articles. Hopefully, future studies will elucidate these mechanisms.

The inflammatory non-suppurative process seen histologically supports the suspicion of an autoimmune etiology. This notion is further supported by the observation that other autoimmune disorders, e.g. SAPHO syndrome [6] (synovitis, acne, pustulosis, hyperostosis, and osteitis), palmo-plantar pustulosis [13] (localized pustular psoriasis), diabetes mellitus, [6,9] chronic inflammatory bowel disease [13] and psoriasis vulgaris, [13] have been diagnosed in patients with non-suppurative OM.

Obviously, the current understanding of the processes and

predisposing factors leading to the development of OM of the jaw is insufficient. Cases with an apparent infectious focus are logically easier to comprehend than the chronic non-suppurative variants with unknown onset. The developmental factors and phases of both main types (pyogenic and non-suppurative) of OM are certainly not fully understood which is reflected in the variations in treatment approaches. Much more research needs to be done on identifying host factors and possible underlying conditions. OM in medically fit individuals is a rare entity in the developed countries [1]. Speculations have been put forth that maybe a number of OM patients otherwise considered healthy have, in fact an undiagnosed underlying condition predisposing them towards OM. Systemic diseases like diabetes, anemia and malnutrition are causing alterations in host defenses and are known to profoundly influence the course of OM [1].

Non-surgical treatment is in most reported OM cases not sufficient. It is very interesting that NSAIDs in some cases are seemingly sufficient to achieve remission in PCO. The mechanisms of action are as yet undescribed. An understanding of the mechanisms involved might alter the general perception of surgery as a standard PCO treatment modality.

Bisphosphonates are showing remarkable results in treatment of PCO, DSO and DSOM [4-6,16], even in cases of prolonged duration. So far the number of reported cases is very limited and no long-term results are available. Urade et al. report one patient receiving pamidronate, followed for 6 years, showing radiographically confirmed close to normal bone architecture after 3 years and remission for the entire 6 years [4]. Severe adverse effects may occur in long-term treatments with resulting Bisphosphonate-Associated OM of the Jaw (BAOMJ). Consequently, bisphosphonate patients should be monitored. The more potent bisphosphonates are reported to have a more rapid onset of pain relieving properties. Pamidronate and alendronate have 100 to 1000 times higher antiresorptive potencies than clodronate [4]. Current knowledge on bisphosphonate use states that the incidence of BAOMJ is dependent on the potency of the drug, the dosage, the frequency of administration, and the duration of the therapy. Without other risk factors present, BAOMJ is unlikely to develop [26]. The incidence of BAOMJ in non-cancer osteoporosis patients taking orally administered bisphosphonates is on average 1 per 100.000 per year of exposure [26]. Immuno compromised status, surgical procedures, tooth extractions, oral hygiene, infections, glucocorticoids or chemotherapy, and age above 70 years are mentioned as precipitating factors for BAOMJ [26]. To our knowledge no data exist on the risk of patients with OM of the jaw, treated with bisphosphonate, developing BAOMJ. Whether surgical procedures after single infusions of highly potent bisphosphonates in OM patients are advisable, needs to be further investigated. The pathophysiological mechanisms of bisphosphonate interactions in OM are incompletely understood and further studies are needed.

Surgical units have to deal with the concern regarding cost-effectiveness of the different diagnostic and treatment options. Theologie-Lygidakis et al. are of the belief that decortication has the optimal cost-to-benefit ratio when dealing with PCO, as it accomplishes adequate recession of signs and symptoms and the procedure is relatively safe to perform and even repeat without exposing the patient to the morbidity of more aggressive surgical

procedures or the disturbing adverse effects of the to date tried pharmaceutical therapies [14]. PCO has with its chronic and recurrent nature a frustrating treatment resistance. Bevin et al. also support decortication as the preferred surgical treatment as this can be repeated without the high morbidity of aggressive surgery like marginal or segmental resections [9]. These procedures are often advocated based on the high recurrence rate of decortications [9]. Baltensperger et al. finds that repeated surgical procedures on PCO does not provide better results than either a single operation or conservative treatment [6]. PCO has a relatively mild and self-limiting course over time tending towards spontaneous remission, making aggressive surgical procedures like resections seem unnecessary.

Infectious OM of the jaw is in all reported cases treated surgically. Early intervention seems to provide a better prognosis and may be a key factor in avoiding ablative surgical procedures [7].

It is notable that OM of the jaw is often localized, typically affecting only one side of the mandible and very seldom the maxilla or other bone structures of the head. If an immune deficiency is a causing factor, then logically lesions ought to occur more widely distributed. What are the common features of these localized bony structures and which underlying factors may be influencing the development of the disease? Are the same immunological factors present in both the suppurative and non-suppurative types of OM? Is infectious OM simply a matter of invading pathogens overpowering the immune responses, regardless if the patient is immunologically fit or compromised? Most likely both main types of OM are multifactorial and represent a series of events and stages leading to clinical disease. A more precise understanding of disease initiation, progression, and stages would allow a more situation-specific treatment and hopefully a higher rate of consistent successful results. However, identifying these factors represents a huge future challenge.

Conclusion

The current understanding of the processes and predisposing factors leading to the development of OM of the jaw is insufficient. The developmental factors and phases of both main types (pyogenic and non-suppurative) of OM of the jaw are inadequately understood which is reflected in the variations in treatment approaches. Much more research needs to be done on identifying host factors and possible underlying predisposing conditions. Likewise, the understanding of the mechanisms of action concerning treatment drugs, are currently insufficient.

Collecting data from articles has proved difficult because there are a number of OM diagnoses for what seems to be the same condition (clinical and histologic findings are remarkably similar) and the number of patients is often very limited due to the rarity of some forms of OM of the jaw. Hence studies with control groups are rarely seen, making the level of evidence lower. A more widely accepted diagnostic consensus is needed if reported data from future articles are to be used in meta-analyses.

References

- Patel V, Harwood A, McGurk M. Osteomyelitis presenting in two patients: a challenging disease to manage. *Br Dent J*. 2010; 209: 393-396.
- Humber CC, Albilia JB, Rittenberg B. Chronic osteomyelitis following an uncomplicated dental extraction *J Can Dent Assoc*. 2011; 77: b98.
- Nezafati S, Ghavimi MA, Yavari AS. Localized osteomyelitis of the mandible secondary to dental treatment: report of a case. *J Dent Res Dent Clin Dent Prospects*. 2009; 3: 67-69.
- Urade M, Noguchi K, Takaoka K, Moridera K, Kishimoto H. Diffuse sclerosing osteomyelitis of the mandible successfully treated with pamidronate: a long-term follow-up report. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2012; 114: 9-12.
- Eyrich GK, Baltensperger MM, Bruder E, Graetz KW. Primary chronic osteomyelitis in childhood and adolescence: a retrospective analysis of 11 cases and review of the literature. *J Oral Maxillofac Surg*. 2003; 61: 561-573.
- Baltensperger M, Grätz K, Bruder E, Lebeda R, Makek M, Eyrich G. Is primary chronic osteomyelitis a uniform disease? Proposal of a classification based on a retrospective analysis of patients treated in the past 30 years. *J Craniomaxillofac Surg*. 2004; 32: 43-50.
- Krakoviak PA, Alveolar osteitis and osteomyelitis of the jaws. *Oral Maxillofac Surg Clin North Am*. 2011; 23: 401-413.
- Obel G, Krogdahl A, Thygesen T, Godballe C. Juvenile mandibular chronic osteomyelitis: 3 cases and a literature review. *J Oral Maxillofac Surg*. 2013; 71: 305-309.
- Bevin CR, Inwards CY, Keller EE. Surgical management of primary chronic osteomyelitis: a long-term retrospective analysis. *J Oral Maxillofac Surg*. 2008; 66: 2073-2085.
- Kim SG, HS Jang. Treatment of chronic osteomyelitis in Korea. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2001; 92: 394-398.
- Lukošiūnas A, Kubilius R, Sabalys G, Keizeris T, Sakavičius D. An analysis of etiological factors for traumatic mandibular osteomyelitis. *Medicina*. 2011; 47: 380-385.
- Coviello V, Stevens MR. Contemporary concepts in the treatment of chronic osteomyelitis. *Oral Maxillofac Surg Clin North Am*. 2007; 19: 523-534.
- Monsour PA, Dalton JB. Chronic recurrent multifocal osteomyelitis involving the mandible: case reports and review of the literature. *Dentomaxillofac Radiol*. 2010; 39: 184-190.
- Theologie-Lygidakis N, Schoinhoriti O, Iatrou I. Surgical management of primary chronic osteomyelitis of the jaws in children: a prospective analysis of five cases and review of the literature. *Oral Maxillofac Surg*. 2011; 15: 41-50.
- Kaiser D, Bolt I, Hofer M, Relly C, Berthet G, Bolz D, et al. Pediatric Chronic nonbacterial osteomyelitis in children: a retrospective multicenter study. *Rheumatol Online J*. 2015; 13: 25.
- Hino S, Murase R, Terakado N, Shintani S, Hamakawa H. Response of diffuse sclerosing osteomyelitis of the mandible to alendronate: follow-up study by 99mTc scintigraphy *Int J Oral Maxillofac Surg*. 2005; 34: 576-578.
- Hakim SG, Bruecker CW, Jacobsen HCh, Hermes D, Lauer I, Eckerle S, et al. The value of FDG-PET and bone scintigraphy with SPECT in the primary diagnosis and follow-up of patients with chronic osteomyelitis of the mandible. *Int J Oral Maxillofac Surg*. 2006; 35: 809-816.
- Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009; 151: 264-269.
- Marx RE, Tursun R. Suppurative osteomyelitis, bisphosphonate induced osteonecrosis, osteoradionecrosis: a blinded histopathologic comparison and its implications for the mechanism of each disease. *Int J Oral Maxillofac Surg*. 2012; 41: 283-289.
- Lucchesi L, Kwok J. Long term antibiotics and calcitonin in the treatment of chronic osteomyelitis of the mandible: case report. *Br J Oral Maxillofac Surg*. 2008; 46: 400-402.
- Deepak S Patel. Do NSAIDs Impair Healing of Musculoskeletal Injuries? *J Musculoskel Med*. 2011: 207-212.
- Hoggatt J, M.K.S, Singh P, Hoggatt AF, Chitteti BR, Speth JM, et al., Differential stem- and progenitor-cell trafficking by prostaglandin E2. *Nature*. 2013; 495: 365-369.

23. Handschel J, Brüssermann S, Depprich R, Ommerborn M, Naujoks C, Kübler NR, et al. [Evaluation of hyperbaric oxygen therapy in treatment of patients with osteomyelitis of the mandible]. *Mund Kiefer Gesichtschir.* 2007; 11: 285-290.
24. Paim LB, Liphaut BL, Rocha AC, Castellanos AL, Silva CA. [Chronic recurrent multifocal osteomyelitis of the mandible: report of three cases]. *J Pediatr (Rio J).* 2003; 79: 467-470.
25. Deutschmann A, Mache CJ, Bodo K, Zebedin D, Ring E. Successful treatment of chronic recurrent multifocal osteomyelitis with tumor necrosis factor-alpha blockage. *Pediatrics.* 2005; 116: 1231-1233.
26. Wimalawansa, SJ. Bisphosphonate-associated osteomyelitis of the jaw: guidelines for practicing clinicians. *Endocr Pract.* 2008; 14: 1150-1168.