ANTIMICROBIAL AGENTS AGAINST OROFACIAL INFECTIONS.  
A BRIEF REVIEW. 

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1. Acknowledgment
Curious on the current evidence based knowledge of antimicrobial use in orofacial infections, this project raised an opportunity to seek more information. The aim of this paper was to search for existing literature on the field of antimicrobial agents in the dental practice.

This paper is a review of approximately 410 articles found on PubMed. The object was to compare results presented in different articles on the use of antibiotics when treating orofacial infections. A comprehensive literature review is beyond the scope of this review, as the number of pertinent articles is extensive. Therefore, the work of only a selected number of authors is reviewed for the purpose of organizing my understanding of antimicrobial treatment of orofacial infections.

I would like to express my sincere gratitude and appreciation to my mentor, Professor dr. scient. & cand.odont. Lasse A. Skoglund, for his dedicated involvement and important help.
2. Introduction

The earliest evidence of humans using herbs or plants for therapeutic purposes comes from the Neanderthals (Herbs2000.com 2011, Neanderthal 2011). Over 50,000 years ago, the Neanderthals would use herbs and natural substances to kill the bacteria in wounds (Herbs2000.com 2011).

During ancient times more than 3,000 years ago, the Egyptians, the Chinese, and Indians of Central America would use herbs or certain organisms like molds to stop the growth of harmful bacteria (Experiment-resources 2011). It was then that the discovery was made that molds could treat infections. This was the birth of antibiotics. However, at that time they did not understand how the mold could cure infections (Experiment-resources 2011).

Later on, scientists began to search for drugs that would kill the infection-causing bacteria (Experiment-resources 2011). In 1899, the two German physicians Rudolf Emmerich and Oscar Low, were the first to make a medication from microbes. This was the first antibiotic to be used in hospitals (What Is The History Of Antibiotics? 2011).

From the early twentieth century, the scientists have discovered and developed many new antibiotics (Herbs2000.com). In 1929, the Scottish pharmacologist Sir Alexander Fleming discovered that molds have very good antibacterial properties. He named the mold *Penicillium*, and the chemical produced by the mold was named penicillin (Herbs2000.com 2011, Experiment-resources 2011). In 1935, the German pathologist and bacteriologist Gerhard Domagk discovered synthetic antimicrobial chemicals, which he called sulfonamides. During 1940’s and 50’s streptomycin, tetracycline and chloramphenicol were discovered (Herbs2000.com 2011).

Since the first discovery of penicillins, antibiotics have attracted much clinical and pharmacological research, in response to the progressive challenges posted by bacterial infections; identification of new pathogens, the development of resistances to antibiotics, and the discovery of new diseases. Bacterial infections are common in dental practice, and antibiotics have therefore been used extensively in dentistry for the management of orofacial infections (Ellison 2009).
3. Antimicrobial agents and odontogenic diseases

3.1 Antimicrobial therapy and periodontal diseases

Periodontal pathogens
Periodontitis is an inflammatory disease characterized by loss of attachment around the teeth (Lindhe et al. 2003). The importance of meticulous instruction in oral hygiene and mechanical debridement (scaling and root planing) in combating the pathogenic microflora in periodontal diseases has been stated in several studies (Lindhe et al. 2003). Most forms of periodontal disease can be successfully treated by a regimen that includes the institution of careful self performed plaque control and mechanical removal of the supra- and subgingival bacterial deposits (Lindhe et al. 2003). In advanced cases, however, surgical procedures are often performed to make the root surfaces of the teeth more accessible to debridement (Preus & Laurell 2003).

While this approach usually arrests periodontal attachment loss in most patients, periodontal breakdown continues in some individuals despite careful treatment. These forms of periodontitis may involve specific pathogens which cannot be eliminated by mechanical therapy only (Lindhe et al. 2003). The unsuccessful treatment outcome may therefore be due to persistent infection by invasive subgingival bacteria (Lindhe et al. 2003). For example, the periodontal pathogens A. actinomycetemcomitans and P. gingivalis can resist debridement and evade the host response by invading epithelial cells lining the gingival crevice (Burrell & Walters 2008). Studies have also showed that scaling and root planing alone or surgery alone often fail to suppress A. actinomycetemcomitans below detectable levels (Christersson et al. 1985, Renvert et al. 1990, Slots & Rosling 1983, Slots & Listgarten 1988).

Why use antibiotic when combating periodontal diseases?
There is considerable evidence that periodontal disease is an opportunistic infection that is mediated by host response to an overgrowth of mostly anaerobic species within the dental plaque (Loesche et al. 1999).

According to some authors, antibiotics should be used as an adjunct to refractory periodontal disease, advanced periodontitis, rapidly progressing periodontitis and acute periodontal abscess (Preus & Laurell 2003). These types of periodontal diseases represent complex diseases associated with specific bacterial species and specific genetic determinants affecting its pathogenesis, the hosts defense, and thereby the therapy outcomes (Albandar &

Other arguments in favor of combining mechanical debridement with antimicrobial therapy are that studies now show significant clinical benefits of antibiotics. Studies indicate that the addition of antimicrobial agents to mechanical debridement may reduce the need for further treatment, like periodontal surgery. Mechanical therapy has unwanted effects as well, particularly when performed repeatedly; it can damage hard tissues and produce gingival recessions.

The evidence raises the possibility that many forms of periodontal disease can be treated with additional antimicrobial agents directed against the responsible microorganisms.

**Results from studies on the use of different antibiotics in treating periodontal diseases**

**Penicillin**

Treatment outcomes in periodontal disease have traditionally been measured as an arrest in periodontal attachment lost (Lindhe et al. 2003). In some cases we can also see a reduction in probing depths and gain in attachment. We know that mechanical treatment does not eliminate all bacteria from diseased sites completely, and therefore additional antimicrobial therapy is sometimes indicated. Still, a restrictive attitude towards using antibiotics has been recommended, mainly to limit the development of microbial antibiotic resistance in general, and to avoid the risk of unwanted effects of antibiotics.

All penicillins are β-lactam antibiotics and they interfere with the synthesis of the bacterial cell wall peptidoglycan (Felleskatalogen 2011, Rang & Dale 2007, Penicillin 2011). Penicillins are bactericidal and small-spectrum antibiotics, and they are used in the treatment

Although several antibiotics, such as metronidazole, azithromycin, and β-lactam antibiotics combined with β-lactamase inhibitors, are still generally active against pigmented Prevotella species (Wexler et al. 1997), resistance to penicillins is increasing (Walker 1996). In fact, penicillin resistance due to β-lactamase production is common in pigmented Prevotella species (Appelbaum et al. 1990, Jousimies-Somer et al. 1993, Kinder et al. 1986, Könönen et al. 1997, van Winkelhoff et al. 1997).

The various frequencies of β-lactamase production of P.intermedia group isolates may be explained by differences in the geographic locations (Appelbaum et al. 1990). Many investigators have reported β-lactamase production in subgingival periodontal isolates in several countries (Bernal et al. 1998, Dubreuil et al. 2003, Fosse et al. 2002, Herrera et al. 2000, Maestre et al. 2007, van Winkelhoff et al. 1997). Herrera et al. (2000) reported a higher prevalence and a more complex β-lactamase producing microflora in a group of Spanish patients. Handal et al. (2003) showed that β-lactamase activity in subgingival bacteria from refractory periodontitis in Norwegian patients also is a common feature. Eick et al. (1999) found that nine species from subgingival plaque samples, among them four P.intermedia and two P.gingivalis strains produced a β-lactamase.

In a study conducted by Milazzo (2002), β-lactamase production was demonstrated in B.forsythus, Prevotella spp. and in F.nucleatum. Mättö et al. (1999) investigated the β-lactamase production of P.intermedia, P.nigrescens and P.pallens isolates and their in vitro susceptibilities to 6 antimicrobial agents. The results in the present study showed that β-lactamase production was common among the above mentioned species. The authors concluded that therapy with penicillin may not be optimal in infections involving P.intermedia, because of the enzymatic hydrolysis of penicillin due to the β-lactamase production of these species.

Today many bacterial species produce β-lactamases (Heimdahl et al. 1981). Therefore penicillin cannot be recommended for empirical antimicrobial therapy when treating periodontal diseases.

Tetracycline

Tetracyclines are bacteriostatic agents that bind to the 30S subunit of the bacterial ribosome inhibiting protein synthesis (Rang & Dale 2007). They are broad-spectrum antibiotics with
activity against aerobic and anaerobic gram-positive and gram-negative organisms (Fellesskatalogen 2011, Rang & Dale 2007). Numerous clinical and microbiological studies have reported that patients with periodontal diseases show significant improvement in clinical treatment outcomes with 1 g systemically administered tetracycline for 14 days as an adjunct to scaling and root planing (Christersson & Zambon 1993, Genco et al. 1981, Gjermo 1986, Kornman & Robertson 1985, Lindhe & Liljenberg 1984, Slots & Rosling 1983). The favorable results achieved by adjunctive systemic tetracycline in patients with generalized juvenile periodontitis are attributed to the suppression of subgingival A. actinomycetemcomitans (Slots & Rams 1990, Walker et al. 1985).

Tetracyclines and their antimicrobial properties have long been recognized as useful adjuncts in the treatment of periodontal diseases. These agents are now also recognized to have non-antimicrobial properties that may also be therapeutically advantageous (Golub et al. 1991). Tetracyclines have been found to inhibit host collagenase activity; an effect that would be expected to inhibit the connective tissue degeneration, including bone resorption (Golub et al. 1984). These finding have been confirmed recently by Golub et al. (2010).

Some authors suggest that when tetracyclines are used against A.a, 3 weeks of treatment is desirable (Preus & Laurell 2003). Preus & Laurell (2003) underscores that tetracycline should only be used where other antimicrobial agents cannot be used for different reasons, because tetracyclines are the antibiotics to which bacteria develop resistance to the fastest.

Although systemic tetracycline as adjunct to scaling and root planing is able to improve treatment outcomes in many cases, other studies have showed that this therapy fails to eliminate A. actinomycetemcomitans from subgingival areas (Christersson & Zambon 1993, Mandell et al. 1986, Mandell & Socransky 1988, Slots & Rosling 1983, van Winkelhoff et al. 1989, van Winkelhoff et al. 1992).

The reason might be that tetracycline occurs in serum and gingival connective tissues in levels too low to inhibit A. actinomycetemcomitans with its properties to invade tissues (van Winkelhoff et al. 1989). Another reason could be because of the frequent use of tetracyclines in periodontal practice (Preus et al. 1992, Slots & Rams 1990). As a result of this, patients with refractory periodontitis often present with a history of tetracycline therapy and a microflora that is resistant to this antibiotic (Olsvik & Tenover 1993, Walker et al. 1993, Walker et al. 1996). Handal et al. (2003) found that two of the Prevotella isolates in their study were resistant to tetracycline.
Also, some examiners have shown less effect of administration of systemic tetracycline. In one study, 20 individuals received scaling and root planing, with or without adjunctive administration of systemic doxycycline (Feres et al. 1999). Feres et al. could not find significant difference between the two groups.

In another study comparing different antibiotics, doxycycline (200 mg x 1/d for 8 days), metronidazole (500 mg x 2/d for 8 days), clindamycin (150 mg x 4/d for 8 days) or none, doxycycline was found to be the antibiotic with inferior effect (Sigusch et al. 2001).

Xajigeorgiou et al. (2006) also compared different antibiotics. Metronidazole plus amoxicillin, doxycycline and metronidazole were studied in patients with generalized aggressive periodontitis. The investigators could not find any difference between the individuals who received adjunctive doxycycline compared to control group only treated with scaling and root planing (Xajigeorgiou et al. 2006).

**Clindamycin**

Clindamycin is a semi-synthetic lincosamide antibioticum (Rang & Dale 2007, Clindamycin 2011). It is a bacterial protein synthesis inhibitor by inhibiting ribosomal translocation (Felleskatalogen 2011, Rang & Dale 2007). It does so by binding to the 50S rRNA of the large bacterial ribosome subunit (Felleskatalogen 2011). Clindamycin is used primarily to treat infections caused by susceptible anaerobic bacteria and Gram-positive cocci, and has a bacteriostatic effect on the targeted organisms (Felleskatalogen 2011).

Clindamycin is frequently used in dentistry. Positive effects of clindamycin are the ability to penetrate into bone and the negative influence on the formation of biofilms (Eick et al. 2000, Lewis et al. 1995). Beside its bacteriostatic effect, clindamycin can interact directly with cells of the immune system. This was confirmed in a study performed by Eick et al. (2000). The purpose of the study was to determine the effect of clindamycin on the phagocytizing properties of gingival crevicular PMNs obtained from patients with rapidly progressive periodontitis. An enhancement of the intracellular killing of *P. gingivalis* and *A. actinomycetemcomitans* after the addition of clindamycin was found in the control group (Eick et al. 2000).

Eick et al. (2000) suggest that clindamycin therapy therefore is an effective means of treating periodontal disease due to obligate anaerobic bacilli such as *P. gingivalis* and *P. intermedia*. These species are sufficiently susceptible to clindamycin. Handal et al. (2004) observed 100 % susceptibility to clindamycin in all *Prevotella* isolates.
With that being said, Eick et al. (2000) could not however, show any enhancement in bactericidal activity of crevicular PMNs from periodontitis patients (the test group).

Also, *E.corrodens* and *A.actinomycetemcomitans*, both important species in cases of periodontitis, have a natural resistance to clindamycin (Eick et al. 1999). In addition, there have been reports on taste disorders and other adverse effects associated with the use of oral clindamycin (de Groot & van Puijenbroek 2007). According to de Groot & van Puijenbroek 2007 (2007), taste disorders associated with the use of clindamycin can be a primary effect of the chemical compound or a secondary effect due to disturbances in oropharyngeal microflora resulting from its pharmacological action.

**Macrolides**

Macrolides are protein synthesis inhibitors (Macrolides 2011). The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis. They do so by binding reversibly to the P site on the subunit 50S of the bacterial ribosome. This action is mainly bacteriostatic, but can also be bactericidal in high concentrations (Felleskatalogen 2011).

Burrell & Walters (2008) studied the distribution of systemic clarithromycin to gingiva. Clarithromycin is a macrolide, and possesses a broad antimicrobial spectrum, favorable tissue distribution, and a low incidence of adverse effects (Rang & Dale 2007). Clarithromycin also readily penetrates cells to gain access to intracellular pathogens (Burrell & Walters 2008). The results from this study showed that clarithromycin can reach significantly higher concentrations in gingival tissue than in serum, and reaches higher levels in inflamed gingiva than in healthy gingiva (Burrell & Walters 2008). This is because clarithromycin accumulates in phagocytes, monocytes, fibroblasts, polymorphonuclear cells, macrophages and lymphocytes (Burrell & Walters 2008).

Another antimicrobial agent similar to clarithromycin is azithromycin, which also is a macrolide. This antimicrobial agent has similar properties as clarithromycin, in the way that the drug is taken up by neutrophils, macrophages and fibroblasts, and is slowly released by these cells (Hirsch et al. 2010). Azithromycin has a potent antibiotic activity against Gram-negative bacteria, is able to penetrate dental biofilm and has a good periodontal tissue penetration. Other positive properties with this agent are that when administered systemically, azithromycin is concentrated in the periodontal tissues where it is retained for at least 14 days (Hirsch et al. 2010).
Azithromycin has also been tested as an adjunct to scaling and root planing in the treatment of adult periodontitis, in a double-blind, placebo-controlled study (Sefton et al. 1996). In this study, the azithromycin group showed better clinical and microbiological results than the placebo (Sefton et al. 1996).

**Fluoroquinolones**
Fluoroquinolones are bactericidal and they eradicate bacteria by directly inhibit DNA synthesis (Felleskatalogen 2011, Quinolone 2011). Established antibiotics such as some of the above mentioned agents are often not effective enough or show potential for side effects. Therefore, other antimicrobial agents without these disadvantages have also been investigated. Tanner et al. (1994) suggested that the requirements for a good antibiotic could be fulfilled by fluoroquinolones which are effective against the *Pasteurellaeae* family to which *A. actinomycetemcomitans* belongs.

Kleinfelder et al. (2000) investigated the effect of systemic therapy with ofloxacin as adjunct to open flap surgery in patients with *A. actinomycetemcomitans*-associated periodontitis. Ofloxacin was selected from the group of the fluoroquinolones since it showed marked in vitro antibacterial activity against *A. actinomycetemcomitans* (Kleinfelder et al. 2000). Furthermore, the uptake of ofloxacin by resting PMNs appears to be much higher than the uptake of other quinolones (Walters et al. 1999). PMNs may serve as vehicles for transport from the bloodstream to infection sites. By this mechanism, PMNs have the potential to enhance resolution of an infection by increasing the local quinolone concentration at sites most beneficial to the host (Loo et al. 1997).

In the study conducted by Kleinfelder et al. (2000), 25 periodontitis patients with subgingival detection of *A. actinomycetemcomitans* were treated with ofloxacin 2 x 200 mg/day for 5 days as adjunct to open flap surgery. Another 10 patients in the control group received only flap surgery. The systemic use of ofloxacin as an adjunct to periodontal flap surgery resulted in a significant reduction of probing depth and in a significant gain of clinical attachment in periodontitis patients harboring *A. actinomycetemcomitans* (Kleinfelder et al. 2000). Hence, according to Kleinfelder, systemic use of ofloxacin as an adjunct to conventional periodontal therapy might be a valuable alternative for treatment of
A. *actinomycetemcomitans*-associated periodontitis in patients with intolerance to other recommended antibiotics.

Milazzo et al. (2002) compared the in vitro activity of moxifloxacin with that of penicillin, amoxicillin/clavulanate, cefoxitin, erythromycin, clindamycin and metronidazole against isolates associated with periodontal infections. Moxifloxacin is a relatively new oral quinolone with a wide spectrum of activity. Milazzo et al. (2002) concluded that moxifloxacin has good antibacterial activity against periodontal pathogens comparable with that of cefoxitin and amoxicillin/clavulanate, and better than that of clindamycin, metronidazole and penicillin.

Other authors have a more restricted attitude towards recommending fluoroquinolones when treating periodontal diseases. Preus & Laurell (2003) proposes that ciprofloxacin is indicated only when microbiological tests can confirm that a super infection with bacteria like *enterobacteria, pseudomonads or staphylococci* is present. If this is the case, Preus & Laurell recommend ciprofloxacin 500 mg x 2 per day in 10-14 days. They also underscore the importance of mechanical treatment and the use of clorhexidine gel, as a first attempt to eliminate the super infection.

**Metronidazole**

Metronidazole is a nitroimidazole antibiotic with bactericidal effect (Felleskatalogen 2011, Metronidazole 2011). Metronidazole, taken up by diffusion, is transformed to active metabolites that inhibit DNA-synthesis in microorganisms (Felleskatalogen 2011).

Metronidazole is well absorbed when administered via the systemic route (Ings et al. 1975), and has been shown to have a pronounced effect on the subgingival microbiota of periodontal lesions in both humans (Loesche et al. 1981) and dogs (Listgarten et al. 1979). The compound is bactericidal against the anaerobic microorganisms of the subgingival microflora, while large portions of aerobic and facultative anaerobic species are less sensitive (Metronidazole 2011).

Metronidazole interacts with electron transport proteins in anaerobic microorganisms to form derivates which interfere with the normal function of such cells (Müller et al. 1977). Therefore, if the infection is caused by Gram-negative anaerobes, the use of metronidazole might be helpful (Eick et al. 1999). Preus & Laurell (2003) suggest that 1250-1500 mg metronidazole per day for 10 days is effective in the treatment of periodontal diseases associated with *P. gingivalis* and *P. intermedia*.

Loesche et al. (1981) used metronidazole in the treatment of 5 patients with periodontal diseases. The agent was administered in tablet form (3 x 250 mg/day) for 7 days
and was found to have a marked and prolonged effect on the proportion of subgingival microorganisms as well as on some clinical symptoms characteristic of periodontal disease. Similar findings have been reported from experiments in dogs (Heijl & Lindhe 1980, Dahlén et al. 1982).

Loesche et al. (1982) also investigated the use of metronidazole in the treatment of patients with acute necrotizing ulcerative gingivitis. The results showed that metronidazole treatment caused a rapid resolution of the clinical symptoms, which coincided with a significant reduction in the plaque proportions.

Lindhe et al. (1983) conducted a study, where 16 individuals were randomly distributed into two treatment groups. The patients of the test group received metronidazole for 3 periods of 2 weeks each, separated by intervals of 8 weeks. The systemic administration of metronidazole reduced/eliminated clinical signs of inflammatory periodontal disease, and the proportions of spirochetes in the subgingival microflora to very low levels (Lindhe et al. 1983). The observations made in this study are in agreement with findings by Shinn (1965), Duckworth et al. (1966) and Loesche et al. (1981, 1984, 1992).

These findings indicate that the use of systemic metronidazole leads to additional treatment benefits, including a reduced need for surgery, beyond that which can be achieved by debridement alone (Lindhe et al. 1983). Jenkens et al. (1989) reported that systemic metronidazole, either alone or accompanied by debridement, produced a significant clinical improvement after debridement alone had failed. Other investigators have shown that also patients with advanced and/or refractory forms of periodontal diseases respond well to metronidazole (Gusberti et al. 1988, Lundström et al. 1984).

Collectively, these studies indicate that metronidazole is most effective when given to patients with high proportions of anaerobes/spirochetes in their plaques, and when combined with mechanical debridement. This means that if metronidazole were to be of value in the treatment of periodontal diseases, it should be so when strict anaerobes dominate in the subgingival microbiota.

Facultative anaerobes like *E. corrodens* and *A. actinomycetemcomitans*, both important species in cases of periodontitis, have a natural resistance to metronidazole (Eick et al. 1999), and the agent is therefore not recommended as a single therapy when these pathogens are registered. This is one of the reasons why authors started to investigate combination therapy.
**Combination therapy**

Several antimicrobial agents (e.g. tetracycline, metronidazole, amoxicillin clavulanate, clindamycin) have been tested for systemic use in periodontal therapy as single antibiotics (van Winkelhoff et al. 1996). Since the subgingival microbiota in advanced periodontal disease often includes species with different antimicrobial susceptibility, combining antibiotic therapy has been suggested (van Winkelhoff et al. 1989, van Winkelhoff et al. 1992).

Antimicrobial regimens that have successfully been used in patients with *A. actinomycetemcomitans*-associated periodontitis are metronidazole in combination with amoxicillin, in combination with amoxicillin/clavulanate or metronidazole plus ciprofloxacin (Goene et al. 1990, Pavicic et al. 1994). These combined antibiotic strategies as adjuncts to scaling and root planing or flap surgery were able to markedly suppress or eliminate *A. actinomycetemcomitans* from periodontal lesions. However, the increased potential for adverse reactions appears to be the major disadvantage of these combined antibiotic regimens (Idsöe et al. 1968, Roe 1977, Saxon et al. 1987).

**Metronidazole plus amoxicillin**

The rationale for the use of combination therapy in periodontitis is to reduce or even eliminate suspected pathogens that exist within the biofilm. Data from systemic reviews elucidated that the clinical outcomes of probing pocket depth, clinical attachment level change, and risk for additional clinical attachment level loss may benefit from combination therapy (Buchmann et al. 2010). Recently, these suggestions have been confirmed for systemic amoxicillin plus metronidazole in a randomized, placebo-controlled clinical trial (Guerrero et al. 2005).

A combination of metronidazole plus amoxicillin used as an adjuvant to mechanical periodontal therapy was also successful in the treatment of advanced and refractory periodontitis (Goené et al. 1990, Kornman et al. 1989, Pavicic et al. 1994, Rams & Slots 1996, van Winkelhoff et al. 1992, Xajigeorgiou et al. 2006). It was shown that this regimen suppressed putative periodontal pathogens not only from the periodontal lesions but also from other sites in the oral cavity (Pavicic et al. 1994).

Van Winkelhoff et al. (1989) also reported that mechanical therapy followed by the combination of metronidazole and amoxicillin was very effective in suppressing *A. actinomycetemcomitans* below cultivable levels in a group of 22 patients. The findings of this study are in accord with the results reported by Xajigeorgiou et al. (2006). These authors concluded that adjunctive metronidazole plus amoxicillin is effective in aggressive periodontitis patients.
Buchmann et al. (2010) conducted a study to investigate the short-term effects of nonsurgical therapy (scaling and root planing/SRP) on the subgingival microbiota in chronic and aggressive periodontal disease. 97 patients underwent scaling and root planing and received either systemic metronidazole plus amoxicillin or were treated with SRP along with placebo tablet. The investigators stated that nonsurgical therapy resulted in both a suppression and early elimination of pathogens immediately after completion of active treatment (Buchmann et al. 2010).

In another study conducted by Berglundh et al. (1998), they looked at the effect of systemic administration of metronidazole and amoxicillin as an adjunct to mechanical therapy in patients with advanced periodontal disease. 16 individuals participated and 4 different treatment groups were formed; group 1: antibiotic therapy but no scaling, group 2: antibiotic therapy plus scaling, group 3: placebo therapy but no scaling, group 4: placebo therapy plus scaling.

The findings of the present clinical trial demonstrated that in patients with advanced periodontal disease, systemic administration of metronidazole plus amoxicillin resulted in an improvement of the periodontal conditions, elimination of putative periodontal pathogens (such as A. actinomycetemcomitans, P. gingivalis, and P. intermedia), and a reduction of the size of the inflammatory lesion (Berglund et al. 1998).

The antibiotic regimen alone, however, was less effective than mechanical therapy with respect to reduction of BOP-positive sites, probing pocket depth reduction and probing attachment gain. The combined mechanical and systemic antibiotic therapy was more effective than mechanical therapy alone in terms of improvement of clinical and microbiological features of periodontal disease.

In the non-scaled quadrants in the placebo group, there were unchanged signs of gingivitis and probing pocket depth, but a significant further loss of probing attachment. In addition, the subgingival microbiota as well as the connective tissue lesion remained unchanged both in terms of quantity and quality (Berglundh et al. 1998).

The finding that self-performed, supragingival plaque control as a single measure was insufficient to prevent further attachment loss, is in agreement with findings presented by Rosling et al. (1997). The results in this study demonstrated that in subjects with advanced and recurrent periodontitis, carefully practiced supragingival plaque control was insufficient to prevent disease progression (Rosling et al. 1997).

Berglund’s observation that the antibiotic regimen altered the subgingival microbiota is in agreement with findings by Pavicic et al. (1994). Pavicic et al. demonstrated that
amoxicillin enhanced the uptake of metronidazole and that this combination of antibiotics increased the antimicrobial range. A total of 48 subjects with A.a-associated periodontitis participated in this study. After the initial therapy of mechanical debridement and oral hygiene instructions, all patients received 250 mg x 3 metronidazole plus 375 mg x 3 amoxicillin for 7 days.

The results indicated that mechanical debridement followed by metronidazole/amoxicillin therapy is able to suppress *A. actinomycetemcomitans* below cultivable levels (Pavicic et al. 1994). Furthermore, they concluded that recurrence of *A. actinomycetemcomitans* to detectable levels by this therapy rarely occurs.

Preus & Laurell (2003) suggest the following combination therapy when treating *A.a*-associated periodontal disease: metronidazole 750 mg per day plus amoxicillin 1250 mg per day for 8 days.

**Conclusion**

Mechanical removal of bacterial deposits on subgingival root surfaces is still the key intervention to treat periodontal diseases, and the use of systemic antibiotics should be restricted to specific groups of periodontal patients, for example those with highly active disease or a specific microbiological profile (Asikainen et al. 2001). The different susceptibilities of these pathogens to antimicrobial agents make therapy very difficult. Microbiological testing has thus been advocated to identify subjects that harbor these organisms (Finegold 1985, Mombelli 2005, Mombelli 2006, Preus & Laurell 2003).

It is recommend that antibiotics should be used as an adjunct to the treatment of aggressive and severe chronic forms of periodontitis only after subgingival debridement has occurred (Herrera et al. 2008).

Antimicrobial agents alone are unlikely to be effective in the presence of subgingival calculus (Slots et al. 2000). Studies show that we should quantitatively reduce the mass of bacteria, which otherwise may inhibit or degrade the antimicrobial agent. Second, we should mechanically disrupt the structured bacterial aggregates that can protect the bacteria from the agent. This underscores the importance of subgingival mechanical debridement.

Also, because most periodontal pathogens are endogenous to humans, the use of antibiotics may result in suppression rather than elimination (Buchmann et al. 2010). Therefore, periodontitis patients need to be controlled regularly after the completion of the debridement procedures in order to avoid recurrence of the disease (Preus & Laurell 2003).
Not all patients benefit equally from antibiotics because they display different microflora and harbor individual susceptibilities against key microbiota. Therefore, elimination or persistence of pathogens after antibiotic usage is an unpredictable event depending on the individual host-pathogen relationship.

3.2 Antimicrobial therapy and odontogenic abscesses

What is an abscess?
An abscess is a localized collection of bacteria, inflammatory cells and tissue breakdown products, which collectively is called pus. It originates when pulpal tissues initiate an inflammatory response to trauma or caries and may eventually lead to pulpal necrosis (Matthews et al. 2003). From this point, the inflammation may become chronic or exacerbation can occur with the formation of a clinical abscess. The formation of pus leads to an increase in tissue pressure, bone resorption, and the pus outbreak through the bone underneath the periosteum into the tissue spaces (Chow et al. 1978, Skucaite et al. 2009).

Dentoalveolar abscesses consist of two main types: the endodontic (periapical) abscess formed after necrosis of the dental pulp, and the periodontal abscess formed after infection of the periodontal tissues by bacteria of the subgingival microbiota (Dahlén 2002). The periodontal abscess is an acute lesion, resulting in rapid destruction of tooth support structures (Herrera et al. 2000).

An abscess that only involves soft tissue is termed cellulitis. The spreading may also involve bone (osteitis) or the bone marrow (osteomyelitis) (Chow et al. 1978). A phlegmon results when an acute infection is not confined as in the case of abscess (Abscess and Phlegmon 2011, Flegmone 2011). Dental abscesses and abscesses in general expand through tissue providing least resistance by forming a sinus tract or a fistula (Dahlén & Frandsen 2002).

Periodontal abscesses occurring in periodontal pockets have been explained by different etiological theories:

1. Exacerbation of a pre-existing periodontitis (Fine 1994, Dello Russo 1985)
2. Inappropriate periodontal therapy, mainly prophylaxis or scaling, which can leave calculus in the deeper parts of the pocket (Dello Russo 1985, Carranza 1990).
Microflora


Herrera et al. (2000) conducted a study where the purpose of the study was to investigate the prevalence of pathogens in periodontal abscesses (Fig. 1). The results were as following:

![Prevalence of each studied pathogen in periodontal abscess (Herrera et al. 2000)](image)

A.a. = *A. actinomycetemcomitans*  
P.g. = *P. gingivalis*  
P.i. = *P. intermedia*  
B.f. = *B. forsythus*  
P.m. = *P. micros*  
C.r. = *C. rectus*  
F.n. = *F. nucleatum*  
P.mel. = *P. melaninogenica*

According to Brook (2002), the main anaerobes are pigmented *Prevotella* and *Porphyromonas, Fusobacterium* spp. and *Peptostreptococcus* spp. The most commonly isolated aerobes and facultative bacteria are *Streptococcus pyogenes* and *Staphylococcus aureus*. Külekci et al. (1996) investigated aspirates of pus from dentoalveolar abscesses, and
presented the same results as Brook (2002), with Prevotella spp., Peptostreptococcus spp. and Streptococcus spp. being the predominant isolates.

The bacteriological data reported by Kuriyama et al. (2000) are in agreement with these studies. Kuriyama et al. reported that a mixed infection of strict anaerobes with facultative anaerobes was observed most often in dentoalveolar infections.

Lewis et al. (1990) also showed similar results; the microflora is predominately involving CO₂-dependent streptococci, strictly anaerobic Gram-positive cocci and strictly anaerobic Gram-negative bacilli. Newman & Sims (1979) found that 63.1 % of the flora was strict anaerobes. Topoll et al. (1990) reported 59.5 % of strict anaerobes, whereas Herrera et al. (2000) calculated 45.1 %.

In conclusion, it is generally accepted that the microflora of acute dental abscesses is usually polymicrobial with a predominance of strict anaerobes. Only with an understanding of the oral environment, the organisms, and their synergistic existence, can intelligent antibiotic choices be made for the treatment of odontogenic infections (Moenning et al. 1989).

**Treatment of abscesses**

Most dentoalveolar infections arise from overgrowth of normal commensals within the oral cavity as a result of changes in local environmental conditions, leading to opportunistic infections (Ellison 2009). As mentioned above, Dentoalveolar infections are not caused by a single microorganism but are mixed infections, and there is a progression of the microbial species as the infection develops reflecting ecological changes in the affected site (Dirks & Terezhalmy 2004, Marsh & Martin 1999, Pallasch et al. 1993).

Mechanical removal of necrotic infected tissues and surgical drainage are the most important treatment steps (Chow et al. 1978). Some authors restrict the use of antibiotics to specific situations, such as systemic involvement (Ahl et al. 1986), need of premedication, diffuse infection, and difficulties to achieve drainage (Lewis et al. 1987). Antibiotic therapy is generally indicated in case of systemic symptoms and to limit the spread of the infection (Dahlén 2002, Epstein & Scopp 1977). For example, bacterial metabolites, along with endotoxins and exotoxins, may enter the blood stream. These affect the thermoregulatory centre in the hypothalamus leading to an increased body temperature (Ellison 2009).
Drainage of an abscess allow the release of pus, reduce the overall number of microorganisms, decrease the tissue pH, increase oxygen diffusion and allow antibiotics to penetrate (Ellison 2009). This is followed by removal of the cause of the infection, which include proper endodontic treatment, and adjunctive antibiotic therapy if needed. In circumstances where adequate drainage cannot be achieved, the role of antibiotic therapy is of even greater significance (Kuriyama et al. 2005, Kuriyama et al. 2007).

Systemic antibiotic therapy prevents the infection from spreading and it acts in places that mechanical treatment cannot reach (Dahlén & Frandsen 2002, López-Píriz et al. 2007). For the antibiotic to be successful in overcoming the associated systemic symptoms, it must be active against the microorganisms present, be sensitive to those bacteria and be given in adequate dose, frequency and duration to aid resolution of the systemic symptoms (Brook & Foote 2005, Ellison 2009).

**Results from studies on the use of different antibiotics in treating odontogenic abscesses**

**Penicillin**

All penicillins are β-lactam antibiotics and are used in the treatment of bacterial infections caused by susceptible, usually Gram-positive, organisms (Felleskatalogen 2011).

Among the systemic antibiotics employed in the treatment of acute abscesses, penicillin is by far the most common (Genco 1991, Gill & Scully 1988, Gilmore et al. 1988, Lewis et al. 1989, Warnke et al. 2008). This is because of its historical effectiveness, minimal toxicity, and relatively low cost (Moenning 1989). Phenoxybenzylpenicillin (250 mg 6 hourly) has traditionally been regarded as the antimicrobial therapy of choice for patients with acute dentoalveolar abscess (Barker et al. 1987, Gill & Scully 1988, Lewis et al. 1989), and erythromycin for those with a known hypersensitivity to penicillin.

Although the predominance of strict anaerobes in oral infections would make metronidazole a logical choice, *S. milleri*, which is resistant to metronidazole, is frequently isolated in the flora (Lewis et al. 1990). Therefore despite the occurrence of penicillin-resistant anaerobes, microbiological information would support the use of penicillin.

Baumgartner & Xia (2003) performed antibiotic susceptibility tests on a panel of bacteria isolated from endodontic infections. Each of the 98 species of bacteria was tested for antibiotic susceptibility to a panel of six antibiotics. The antibiotics were penicillin V (Pen V), amoxicillin (Amox), amoxicillin and clavulanic acid (Amox/Clav), clindamycin (Clin),
metronidazole (Met) and clarithromycin. Baumgartner & Xia (2003) found the following percentages of susceptibility for the 98 microbial species studied (Fig.2):

![Figure 2. The percentages of susceptibility for 98 species (Baumgartner & Xia 2003).](image)

The results showed that most of the root canal microbiota is susceptible to penicillins. This makes them the drug of choice to be used in infections of endodontic origin (Baumgartner & Xia 2003, Skucaite et al. 2009).

Fouad et al. (1996) conducted a study where the purpose of the study was to examine the effect of penicillin supplementation on reduction of symptoms and the course of recovery of localized acute apical abscess after emergency endodontic treatment. 32 patients were divided into three groups: (1) active group, (2) placebo group, (3) neither medication group. In this study however, the authors found that the administration of penicillin did not provide a clinically significant improvement in the course of recovery of patients with localized acute apical abscess, and there were no significantly differences between the three groups. The same results were presented by Henry et al. in 2001 and Keenan et al. in 2009.

Eick et al. (1999) investigated the activity of penicillin, amoxicillin, cefoxcin, clindamycin, doxycycline, metronidazole and ciprofloxacin. The purpose of their study was to determine MICs of commonly used antibiotics against oral bacteria. Compared with bacteria obtained from subgingival plaque samples, species isolated from odontogenic abscesses showed a higher resistance to the antimicrobials tested. Eick et al. also found that nine species from subgingival plaque samples, among them four *P. intermedia* and two *P. gingivalis* strains produced a β-lactamase.
Amoxicillin and Co-amoxiclav

Of the penicillins, amoxicillin is particularly well absorbed, achieves high concentration at sites of acute infection (Boon et al. 1982, Bresco et al. 2006) and has been used successfully in a short course high-dose form of therapy (Lewis et al. 1986). However the basic cost of a standard course of amoxicillin (250 mg 8 hourly for 5 days) is approximately 10 times that of a standard course of penicillin. This has obviously implications when deciding on antimicrobial prescription policies.

Reports showing that a high percentage of periodontal pockets and abscesses harbor β-lactamase producing bacteria (Lewis et al. 1995, Van Winkelhoff et al. 1997, Walker et al. 1987), have lead to the use of amoxicillin plus clavulanic acid (Lewis et al. 1993, Sobottka et al. 2002, Warnke et al. 2008). Amoxicillin has been widely used in Japan and the UK, largely because of its better absorption from the gastrointestinal tract compared with other oral penicillin agents (Kuriyama et al. 2005, Martin et al. 1997).

Lewis et al. (1993) conducted a randomized, operator-blind, comparative clinical trial, where they studied the efficacy of co-amoxiclav and penicillin V. A total of 79 patients participated, and were divided into two groups. One group received 250 mg amoxicillin plus 125 mg clavulanic acid every 8 hours in 5 days, and the other group received 250 mg penicillin V every 6 hours in 5 days. Symptoms improved in all patients following start of treatment, however those receiving co-amoxiclav recorded a significantly greater decrease in pain during the second and third day. Also, penicillin-resistant organisms were isolated from 5 patients.

Macrolides

Erythromycin is regarded as the drug of choice for treatment of dental infections in patients with a known hypersensitivity to penicillin (Heimdahl et al. 1983, Josefsson et al. 1985, Lewis et al. 1995, Martin et al. 1997). However, it has been noted that erythromycin is not effective against anaerobes such as *Fusobacterium* (Kuriyama et al. 2000, Limeres et al. 2005). Kuriyama et al. (2000) reported in a study that erythromycin had poor antimicrobial activity against *Fusobacterium*. Furthermore, erythromycin was ineffective against viridians streptococci.

It has been demonstrated that *Streptococcus* and *Fusobacterium* are more frequently isolated from severe odontogenic infections than from milder infections (Heimdahl & Nord 1985). The results of this study suggest that erythromycin may be effective against mild or
moderate infections in people with penicillin allergies, but it may not be suitable in cases of more severe infections or infections involving anaerobes. These recommendations are suggested by Kuriyama et al. (2000).

Newly developed macrolides have shown better antimicrobial against gram-negative bacteria, than erythromycin. Among this newer generation of macrolides, azithromycin has attracted a lot of attention due to its pharmacokinetic properties and its high concentration in infection sites. Macrolides, because of their spectrum of activity and pharmacokinetic characteristics of high penetration into soft tissues, such as the gingiva and dental pulp, are frequently used in dental practice (Lo Bue et al. 1993).

Azithromycin may have advantages in the treatment of odontogenic infections, because of its in-vitro and in-vivo activity against the major dental pathogens. Its pharmacokinetic features ensure much higher and sustained tissue concentrations compared with other antibiotics of the same and different classes. The uptake and transport of azithromycin within macrophages, and its release during bacterial phagocytosis, may augment the concentrations of azithromycin at the site of infection (Lo Bue et al. 1993).

An open, randomized clinical trial comparing the efficacy of azithromycin and spiramycin was conducted Lo Bue et al. (1993). 60 patients with odontogenic infections were randomized into two treatment regimens: 30 patients received azithromycin capsules 500 mg/day for 3 days and the remaining 30 received spiramycin tablets 3 000 000 units per day for 7 days, all in conjunction with surgery. The authors concluded that there was a more rapid resolution of symptoms in the group treated with azithromycin.

Herrera et al. (2000) compared the efficacy of azithromycin to that of co-amoxiclav. The aim of this short-term, open parallel longitudinal clinical study was to compare the clinical and microbiological efficacy of two different antibiotic regimes in the treatment of acute periodontal abscesses. The results showed that both antibiotic regimes were effective in the short-term treatment of acute periodontal abscesses.

Clarithromycin is a macrolide and analogue of erythromycin. It has been recommended as an alternative to erythromycin because it is effective against facultative and anaerobic, which are resistant to erythromycin. In addition, food has no effect on the absorption of clarithromycin, and it only needs to be taken twice a day with less gastric upset than erythromycin.
Clarithromycin seems to have efficacy, but it is still considered an antibiotic under investigation because the minimum inhibitory concentration has not been established.

**Metronidazole**

Kuriyama et al. (2007) reported that metronidazole is a useful alternative in combating the anaerobic bacteria involved in dentoalveolar infection. Roche et al. (1997) also found anaerobes from odontogenic abscesses to be highly susceptible to metronidazole. The same results were presented by Ingham et al. (1977) and Lewis et al. (1995). Lewis et al. (1995) also showed that metronidazole is effective against strictly anaerobic bacteria. However, since the flora of acute dentoalveolar abscesses are polymicrobial, appearance of facultative bacteria such as S. milleri makes the use of metronidazole inappropriate in these cases (Lewis et al. 1995), at least as a single regimen.

**Clindamycin**

Clindamycin is an effective antibiotic against strict anaerobes including β-lactamase-producing bacteria. The findings of Kuriyama et al. (2000, 2007) confirmed that clindamycin is effective against strict anaerobes, particularly against pigmented and nonpigmented Prevotella.

Clindamycin produces high alveolar concentrations, and bacterial activity is achieved clinically with the usual recommended dose. In addition, clindamycin might increase host defense potential and inhibit β-lactamase production. Thus, clindamycin would be effective in the treatment of infections. However, because of its propensity to cause antibiotic-associated colitis, it has not been widely used in more routine cases of mild to moderate infections (Heimdahl & Nord 1985, Kuriyama et al. 2000, Kuriyama et al. 2007, Lewis et al. 1995, Limeres et al. 2005). Kuriyama et al. (2000) recommend clindamycin for the treatment of severe infections, or in cases in which penicillin therapy has failed.

The efficacy of clindamycin and phenoxymethylpenicillin in the treatment of orofacial infections was compared in a randomized study where 60 patients participated (von Konow et al. 1992). 30 patients received clindamycin 150 mg every 6 h for 7 days, and 30 patients received phenoxymethylpenicillin 1 g every 12 h for 7 days. The authors could not find any statistically significant difference between the two therapy regimes.
**Fluoroquinolones**

Moxifloxacin is a quinolone compound, which has shown good pharmacokinetic properties, such as high concentrations in bone tissue (Al-Nawas et al. 2009). The pharmacokinetic properties allow a single dose treatment per day. This reduces costs and enhances the patient’s compliance. Besides these promising features, its clinical effect has yet to be proven when it comes to treating dental abscesses, and the long-term development of the resistance situation should be carefully kept in mind (Al-Nawas et al. 2009). Their poor activity against anaerobes will limit their value in treatment of oral infections (Moenning et al.1989).

**Conclusion**

Understanding of the microorganisms responsible for dentoalveolar infections and their susceptibility to various antibiotic agents has progressed significantly. In addition, increasing resistance to antibiotics has led to the need for more appropriate prescribing and to review whether prescribing antibiotics is required at all (Ellison 2009).

The definitive treatment of dentoalveolar abscess is drainage and removal of the cause of the infection. In the majority of cases this is the only treatment required (Brennan et al. 2006). However, if the patient is showing signs of systemic illness as a result of their dentoalveolar infection, or are significantly immunocompromised, the adjunctive therapy with antibiotics may be indicated (Ellison 2009). Clinical signs of fever, trismus, significant regional lymphadenopathy, gross facial swelling, closure of the eye, dysphagia, tachycardia and rigors should be regarded as indicators of systemic response to infections and adjunctive therapy is always indicated (Ellison 2009). Effective drainage to reduce the number of bacteria, promote aerobic conditions and optimize a return to health may be the most important part of the process of abscess resolution (Ellison 2009).

Ellison describes a few guidelines in her article from 2009. Infections derived from the periodontal tissues are anaerobic in nature and metronidazole is the antibiotic of choice. Furthermore, Ellison states that infections derived from periapical tissues are mixed infections, but predominantly anaerobic, and are most appropriately treated with amoxicillin, metronidazole or clindamycin. With regards to dosage, Ellison suggests that the lowest possible effective dose should be used. In order to achieve sufficient concentration of antibiotic in the tissues, the blood concentration should exceed the MIC by a factor of four. A dose of 250 mg x 3/day amoxicillin, 200 mg x 3/day metronidazole or a dose of 150 mg x 4/day clindamycin will be sufficient to achieve the required blood concentration.
Other authors recommend β-lactam antibiotics as the first-line agent for the treatment of orofacial odontogenic infections because they work well against the specific bacterial causative agents of orofacial odontogenic infections with a very low incidence of adverse effects (Baker & Fotos 1994, Gill & Scully 1990, Heimdahl & Nord 1985, Kuriyama et al. 2000, Moenning et al. 1989). In addition, treatment with β-lactam antibiotic is cost-effective. Penicillins are also among the few antibiotics that are indicated when treating odontogenic infections in patients that are pregnant (Sá del Fiol et al. 2005).

A problem with antimicrobial therapy with β-lactam antibiotics is the increasing rate of β-lactamase production, which leads to treatment failures (Heimdahl et al. 1980, von Konow et al. 1990, Lewis et al. 1995). Heimdahl & Nord (1985) and Kinder et al. (1986) have noted that the use of penicillin is associated with the emergence of β-lactamase producing bacteria. The prevalence of penicillin resistance within the flora of acute dental abscess is believed to be approximately 5% (Heimdahl & Nord 1985, Lewis et al. 1989, Lewis et al. 1993, von Konow & Nord 1983, Ranta et al. 1988).


Kuriyama et al. (2000) showed in their study that there was a correlation between the prevalence of the isolation of β-lactamase-producing bacteria and the duration of the past administration of β-lactam antibiotics. They found that β-lactamase-producing bacteria were isolated more frequently, as the administration duration increased. The present study suggests that if patients with orofacial odontogenic infections have already received β-lactam antibiotics for three days or more, regardless of the type of antibiotic or the route of administration, it should be assumed that β-lactamase-producing bacteria are present in the lesion and are associated with infection progression (Kuriyama et al. 2000).

Therefore, the authors recommend that the prescription of penicillins is suitable if the patient has not received β-lactam antibiotics in the course of the infection. If the patient has received antimicrobial therapy with β-lactam in the course of the infection for a duration of 3 days or more, it should be assumed that β-lactamase-producing bacteria may occur or be present in the still-existing lesion. In such cases, β-lactamase-stable β-lactam antibiotics or...
non β-lactam antibiotics such as clindamycin or macrolide are recommended (Kuriyama et al. 2000).

From a clinical point of view, erythromycin, for patients known to be hypersensitive to penicillins, should remain antibiotic of first choice for management of acute suppurative oral infections (Lewis et al. 1995, Sundqvist & Haapasalo 2002). On the rare occasions that patients fail to respond to this initial treatment, alternative antibiotics should be considered (Baker & Fotos 1994, Gill & Scully 1990, Heimdahl & Nord 1985, Kuriyama et al. 2000, Lewis et al. 1995, Moenning et al. 1989).

Incorrect antimicrobial use can lead to a selection of resistant bacteria species in the biofilm, in addition to side effects and ecological alterations in the host (López-Píriz et al. 2007, Takahashi et al. 1998). The increasing resistance of anaerobic bacteria to some widely used antibiotics for treatment of oral infections ensures the need of monitoring susceptibility patterns (Skucaite et al. 2009).

3.3 Antimicrobial therapy and osteomyelitis of the jaws

What is osteomyelitis?

Osteomyelitis can be defined as an inflammatory condition of the bone, which begins as an infection of the medullary cavity, rapidly involves the haversian systems, and extends to involve the periosteum of the affected area (Topazian et al. 1994). Bacteremia, dental infections, infections of the oral cavity, trauma, or surgery are the major predisposing factors for this infection (Malincarne et al. 2006).

Bone necrosis and bone destruction occur early in the course of osteomyelitis, leading to a chronic process and eliminating the hosts ability to eradicate the pathogens. Osteomyelitis most commonly results from bacterial infections, although fungi, parasites, and viruses can affect the bone and marrow (Prasad et al. 2007). Conditions altering the vascularity of the bone such as radiation, malignancy, osteoporosis, osteopetrosis, and Paget’s disease can predispose to osteomyelitis (Prasad et al. 2007).

Abrupt onset of symptoms and signs during the initial stage of infection indicates an acute osteomyelitis. If this phase passes without complete elimination of infection, chronic osteomyelitis can become apparent (Prasad et al. 2007).

Chronic osteomyelitis is a distressing bone disease often characterized by subsidence of systemic symptoms but with one or more foci of pus, infected granulation tissue or sequestra still lodged in the bone (Alonge et al. 2003, Euba et al. 2009). Chronic osteomyelitis
can be primary, when it arises from failed treatment of acute haematogenous osteomyelitis or secondary, when it is caused by trauma to the bone, open fractures or from post-operative infection (Bartkowski et al. 1998).

**Microbiology of osteomyelitis**

Alonge et al. (2003) did a study where the bacteria samples from 60 patients with chronic osteomyelitis were cultured. The results showed that *Staphylococcus aureus* is the single most common microorganism isolated in about 60% of cases, but the isolate is often a mixed flora particularly in secondary chronic osteomyelitis. Calhoun et al. (1988), Mader et al. (1999) and Waldvogel et al. (1970) have also shown that the microflora in osteomyelitis is polymicrobial, and the organism most commonly isolated is *Staphylococcus aureus*.

**The role of antimicrobial therapy in the treatment of osteomyelitis**

Bone infections are difficult to treat, and the therapeutic success depends greatly on the diffusion of antibiotics into the bone tissue (Cachovan et al. 2009). Treatment of osteomyelitis is particularly challenging and involves adequate antimicrobial therapy and surgical debridement of all necrotic bone and soft tissues (Landersdorfer et al. 2009). Despite great advances in antimicrobial therapy, osteomyelitis in the head and neck is a difficult disease to treat, partly because of the anatomical region and also because of esthetic considerations (Fraimow 2009).

As bone is less vascularized tissue than for example, the lungs or skin, it is particularly important to investigate the bone penetration of an antibiotic before using the agent in patients with bone diseases. The presence of pus and ischemic regions (sequester) may further decrease blood circulation (Landersdorfer et al. 2009). The composition of bone is different from that of other tissues, and it is difficult to predict whether agents showing good penetration into other tissues will also achieve high concentrations in bone (Landersdorfer et al. 2009).

Antibiotics in the systemic circulation reach the capillaries in bone and, depending on the chemical profile and molecular size, pass through the capillary walls to enter the fluid space (Cachovan et al. 2009). The penetration of antibiotics into sites outside the vascular circulation is dependent upon factors such as serum pharmacokinetics, protein binding, lipid solubility, ionization state, active transport, passive diffusion, and degree of inflammatory...

Effective antimicrobial therapy is an essential component of most curative treatment regimens for osteomyelitis. In acute osteomyelitis, appropriately targeted antimicrobial therapy alone without other therapeutic measures may sometimes be adequate to achieve eradication of infecting organisms and cure of infection (Merkesteyn et al. 1997).

However, successful management of more severe cases of acute or chronic osteomyelitis generally requires a combination of targeted antimicrobial therapy to eradicate infectious microorganisms and surgical interventions for debridement of necrotic and devitalized tissue, drainage of abscesses, and removal of infected bone (Chow et al. 1978, Fraimow 2009, Hudson 1993, Marx 1991, Topazian 1994).

Antimicrobial therapy is indicated when infection has perforated the cortex and has spread into the surrounding tissue (Isla et al. 2005). Furthermore, it is important to consider antimicrobial therapy if there are signs of systemic involvement. The clinical signs of systemic involvement are pyrexia, lymphadenopathy, difficulty in swallowing, and lockjaw (Dirks & Terezhalmy 2004, Jimenez et al. 2004).

Results from studies on the use of different antibiotics in treating osteomyelitis

Penicillin


*Staphylococcus aureus* remains the predominant pathogen isolated in all forms and stages of osteomyelitis (Pontzer & kaye 1984). Therefore, β-lactam antimicrobials remain the drug of choice for non-allergic patients with methicillin-susceptible *Staphylococcus aureus* (MSSA) infections (Fraimow 2009). However, less than 5% of *S. aureus* is still susceptible to
penicillin. For such strains, intravenous penicillin G is used at doses of 3 to 4 million units every 4 to 6 hours. For other MSSA, the penicillinase-resistant penicillins given intravenously have traditionally been considered the drug of choice (Lew & Waldvogel 2004).

**Vancomycin**
Vancomycin is recommended for the treatment of MRSA osteomyelitis (Lew & Waldvogel 1997). The use of vancomycin for treatment of osteomyelitis has increased dramatically with the emergence of MRSA, which now comprises the majority of *S.aureus* infections seen in hospitals throughout all regions of the United States (Shorr 2007). Retrospective studies have demonstrated higher relapse rates after vancomycin compared with those after a β-lactam for non-MRSA bone infections (Tice et al. 2003). One consequence of increasing vancomycin use is emergence of strains with decreased vancomycin susceptibility (Kollef 2007, Shorr 2007).

**Clindamycin**
Clindamycin is recommended for long-term oral therapy in bone infections with susceptible pathogens (Lew & Waldvogel 2004), and because of its activity against anaerobes, clindamycin has also been recommended for use in anaerobic bone infections (Brook & Foote 2005, Bystedt et al. 1978, Darley et al. 2004, Deodhar et al. 1972, Dirks & Terezhalmy 2004, Finegold et al. 1977, Trampuz & Zimmerli 2006).

Clindamycin has excellent bone penetration (Bystedt et al. 1978) and oral bioavailability, and performed as well as β-lactam monotherapy in the rabbit osteomyelitis model. It has been used successfully for *S. aureus* osteomyelitis in both children and adults (Kaplan et al. 1982, Norden et al. 1986, Rodriguez et al. 1977). However, it is difficult to interpret results for clindamycin, as the available studies are quite old. Most bone penetration studies of clindamycin were conducted in the 1970s (Landersdorfer et al. 2009).

In summary, the results of studies of clindamycin suggest similar or slightly higher penetration compared with β-lactams (Landersdorfer et al. 2009). These studies only compared clindamycin with the other drugs that were available at the time, before the development of comparably newer antibiotics such as the quinolones, linezolid and azithromycin, which all show high tissue penetration (Landersdorfer et al. 2009). Concerns about an association with pseudomembranous colitis have limited its use in elderly patients as well (Darley et al. 2004).
**Linezolid**

Several newer agents with good in vitro and in vivo activity against MRSA have recently been introduced (Lovering et al. 2002). One of the best studied of these is linezolid (Lovering et al. 2002). Linezolid is a synthetic antibiotic belonging to a new class of antimicrobials called the oxazolidinones (Ament et al. 2002). Linezolid is active against *S. aureus* including nearly all MRSA strains, and it has nearly 100% oral bioavailability and demonstrates good bone penetration (Lovering et al. 2002).

Linezolid disrupts bacterial growth by inhibiting the initiation process in protein synthesis. This site of inhibition occurs earlier in the initiation process than other protein synthesis inhibitors (e.g. chloramphenicol, clindamycin, aminoglycosides, macrolides) that interfere with the elongation process (Ament et al. 2002). Because the site of inhibition is unique to linezolid, cross-resistance to other protein synthesis inhibitors has not yet been reported (Ament et al. 2002, Ford et al. 1997, Hamel et al. 2000).

Successful treatment of osteomyelitis patients with linezolid has been reported (Rayner et al. 2004). However, clinical experience in osteomyelitis is limited (Lew & Waldvogel 1997). Although the clinical studies show promising results with Linezolid, the side effects outweigh the positive features. Serious toxicities reported with prolonged linezolid therapy include lactic acidosis, syndromes, optic neuritis and peripheral neuropathy (Falagas et al. 2007, Sennevill et al. 2006). Thus, Linezolid is not an ideal agent for very prolonged treatment courses or chronic suppurative therapy (Fraimow 2007).

**Cephalosporins**

In 1982, Daly et al. (1982) performed a study where the ability of cefazolin to cross capillary membranes was studied in normal and osteomyelitic canine bone. These studies suggest that the altered pathophysiology of osteomyelitic tissue and the complex diffusional characteristics of cefazolin enhanced the ability of this agent to cross the endothelial cells lining the capillaries of osteomyelitic bone.

Pinto et al. (1986) conducted a study where the bone penetration of ceftazidine was recorded in cortical and cancellous bone. The results were promising in both infected and non-infected bone. Similar results have been published for cefonicid, and the drug has been recommended in the treatment of osteomyelitis (Pontzer & kaye 1984). Wittmann & Schassan (1980) reported good cefotaxime concentration in infected bone tissue.

The first-generation cephalosporin, cefadroxil, has been shown to have a wide spectrum of activity against both aerobic and anaerobic bacteria, which may be of importance
in orofacial infections (Cumming et al. 1984). Cumming et al. (1984) conducted a study, where the purpose was to evaluate the role of cefadroxil in the management of patients presenting with acute orofacial infections. The results of this study showed that the MICs of cefadroxil for all of the bacteria recovered, were within attainable blood levels.

On the basis of the results presented in this clinical trial, the authors suggested that cefadroxil may be included in the list of possible drugs used in the treatment of acute orofacial infections (Cumming et al. 1984). Third- and fourth-generation cephalosporins have also been used for MSSA infections, though this must be weighed against the impact of their broader spectrum of action and suppression of normal host bacterial flora and impact on resistance (Fitzgerald 1984, Fraimow 2009).

**Fluoroquinolones**

Quinolones have been the center of considerable clinical and scientific interest since their discovery in the early 1960s (Ball 2000). This is because they potentially offer many of the attributes of an ideal antibiotic, combining high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, and a large volume of distribution indicating concentration in tissues (Andersson & MacGowan 2003, Núñez et al. 2009, Stein 1996).

They possess several properties that enable them to distribute rapidly into tissues, namely, a relatively small molecular size, lipid solubility, long serum half-life, and low levels of binding to serum proteins (Gerding & Hitt 1989, Stein 1996).

The fluoroquinolones are established agents in the treatment of osteomyelitis (Lew & Waldvogel 1999, Mader et al. 1999). Most published data are for ciprofloxacin and ofloxacin, though there is clinical experience with newer agents as well (Gerding & Hitt 1989, Lazzerini et al. 2005, Rissing 1997, Stengel et al. 2001). The data for ofloxacin and pefloxacin are limited but suggest that their penetration into bone is excellent (Gerding & Hitt 1989).

One study performed by Cachovan et al. (2009) investigated the levels of moxifloxacin in mandibular bone in rats. The results showed that moxifloxacin has good penetration into bone and muscle tissues in rats, indicating that this agent might be an option for clinical application (Cachovan et al. 2009).

Another study on the penetration properties of moxifloxacin was performed by Malincarne et al. (2006). The results from this study also showed a good penetration of moxifloxacin into both cancellous and cortical bone.

In addition to their high concentrations in bone, the fluoroquinolones ability to penetrate into cells may be advantageous in bone infections, as S.aureus has been shown in vitro to penetrate into and survive in bone cells (Hudson et al. 1995, Jevon et al. 1999). Quinolones have an effect on adherent bacteria, and they can penetrate macrophages and polymorphs (Hooper & Wood 1991).

There are several excellent reviews of trials of quinolone in bone infections, which summarize encouraging results in studies including Gram-positive, Gram-negative and polymicrobial infections (Giammaretellou et al. 1995, Lew & Waldvogel 1997, Oliphant & Green 2002, Rissing et al. 1997, Trichilis et al. 2000). However, there are some negative aspects associated with the use of quinolones. To my knowledge, there are no long-term follow-up data are available when it comes to treating osteomyelitis with fluoroquinolones.

One concern is the adverse effects associated with fluoroquinolones, including central nervous system disorders, photosensitivity, hepatic dysfunction, and rashes (Committee of Infectious Diseases 2006, Oliphant & Green 2002).

Another major concern with fluoroquinolones, as with other antimicrobial drugs, is emergence of resistance on therapy (Committee on Infectious Diseases 2006). Increasing resistance amongst S.aureus has been observed since the introduction of quinolones (Blumberg et al. 1991), and has resulted in the addition of rifampicin to attempt to prevent this occurring during treatment (Darley et al. 2004, Norden 1975, Yourassowsksy et al. 1981, Zinner et al. 1981).

Conclusion
In the treatment of infections, it is evident that adequate antibiotic concentration must be obtained at the site of the infection (Bystedt et al. 1978). Successful treatment of osteomyelitis in the jaws presupposes that concentrations of an antibiotic exceeding the minimum inhibitory concentration (MIC) of microorganisms causing the infection are achieved (Bystedt et al.
In addition to good bone penetration, an antimicrobial agent needs to have adequate activity against the infecting pathogen, and both the pharmacokinetic characteristics of the drug and the anatomical characteristics of the infection sites must be taken into account in order to avoid drug underexposure in the bone (Navarro 2009, Pea 2009).

The diffusion rate of antibiotics into dead bone is sometimes so low that frequently it is difficult to reach the organisms regardless of the external concentration (Hasegawa et al. 2003). This may lead to ineffective antibiotic concentrations at the site of infection despite serum levels indication therapeutic concentration (Prasad et al. 2007).

The presence of increasingly resistant microorganisms is a concern, both in terms of managing the affected patient and the wider cross-infection implications. The increased frequency of antibiotic usage as well as wider variety of antibiotics has resulted in the emergence of resistant organisms, often to multiple antibiotics (Prasad et al. 2007). These are some of the challenges that clinicians have to face. It is therefore important that the dental clinician keep pace with new knowledge concomitantly with maintenance of basic comprehension, and make correct assessment if the condition requires medical referral.

### 4. Antimicrobial therapy and sinusitis

**Pathophysiology of sinusitis**

Sinusitis generally develops as a complication of viral or allergic inflammation of the upper respiratory tract. Edema and mucosal thickening can lead to inadequate drainage of the sinus. This produces stagnation of secretions, pH changes, epithelial damage and reduced oxygen tension, which creates an ideal environment for bacterial growth. The resultant bacterial products retained within the sinus then cause more mucosal thickening, alteration in the cellular architecture and ciliary dysfunction, which may establish a pathogenic cycle of chronic infection (Revonta & Blokmanis 1994).

The most common precursors to sinusitis include bacterial infections, viral upper respiratory infection, sinus obstruction from mucosal edema of inhalant allergies, and anatomic factors such as septal deviations (Anon et al. 2004, Hadley & Schaefer 1997, Kaliner et al. 1997).

Maxillary sinusitis of odontogenic origin may result from periapical infection, periodontal disease, perforation of the antral floor and mucosa with tooth extraction, and displacement of root or foreign objects into the maxillary sinus during a dental or surgical procedure (Abrahams et al. 1996, Anon et al. 2004, Heath 1972).
Microbiology of sinusitis


Anaerobic bacteria emerge as pathogens as the infection becomes chronic (Brook 2005, Evans et al. 1975, Hamory et al. 1979). *S. aureus* and anaerobic bacteria such as *Prevotella* spp., *Porphyromonas* spp. and *Fusobacterium* spp., are also commonly isolated in chronic sinusitis (Brook 2005, Evans et al. 1975, Vakharia et al. 2009).

In chronic sinusitis the etiologic infectious organisms are highly variable, with anaerobic organisms isolated with increased frequency. Brook (1981) reported that 88 % of culture positive cases in sinus infections contained anaerobes, and 32 % were part of a mixed infection. Of the anaerobes approximately 50 % exhibited β-lactamase activity.

Clinical presentation

It is important to accurately diagnose the type of sinusitis a patient has before initiating treatment, as the bacteriology and management of each condition differs significantly. Patient evaluation should start with a thorough history and complete local examination (Pynn & Nish 2008).

Acute sinusitis presents with rhinorrhea that often is purulent, unilateral or bilateral infraorbital tenderness, nasal obstruction, dull headache, intermittent fever, and/or cheek swelling of less than 3 weeks duration (Stankiewicz et al. 1994). Additional signs can include tenderness with chewing, halitosis, and altered sense of smell or taste (Stafford 1990).

Chronic sinusitis is defined as signs and symptoms of sinusitis which persist for more than 12 weeks (Stankiewicz et al. 1994).

The close proximity of the maxillary sinus floor to the root apices of the posterior maxillary teeth may lead to symptoms that suggest dental diseases (Kennedy 1990). Sinus infections of odontogenic origin can be differentiated from infections arising secondary to
upper respiratory tract infections based on the difference in presentation and microbiology (Sandler et al. 1996). This type of sinusitis represents approximately 10% of all cases (Brook 2005, Maloney & Doku 1968).

Inflammation of the sinus lining can produce percussion sensitivity in the molar teeth. However, in the absence of concurrent pulpal disease these teeth will respond vital to pulp testing and will not exhibit thermal sensitivity (Pynn & Nish 2008). In addition, pain that varies with changes in head position is suggestive of sinusitis (Pynn & Nish 2008).

X-ray of the sinuses may be taken to evaluate symptoms of possible sinusitis. An OPG is commonly used to help distinguish uncomplicated sinusitis from other problems that may cause similar symptoms, such as odontogenic infections or jaw joints. However, if sinusitis is suspected and other possible causes are eliminated, computed tomography (CT) scan shows a much clearer picture of the sinuses (Sinus X-ray for Sinusitis).

Management of sinusitis
The management goals for the treatment of sinusitis include control of infection and pain, reduction of tissue edema and facilitation of drainage (Pynn & Nish 2008). When selecting antibiotic therapy for patients with sinusitis, the clinician should consider the severity of the disease, the rate of progression of the disease, and recent antibiotic exposure (Anon et al. 2004). The goal of antimicrobial therapy is to eradicate susceptible organisms in the sinus cavity (Brook & Foote 2005), and to facilitate recovery and prevent septic complications (Brook et al. 2008).

The growing resistance to antimicrobial agents of all respiratory tract bacterial pathogens has made the management of sinusitis more difficult (Brook & Foote 2005). Additionally, factors within the sinus cavity that may enable organisms to survive antimicrobial therapy are: inadequate penetration of antimicrobial agents, a high protein concentration (can bind antimicrobial agents), a high content of enzymes that inactivate antimicrobial agents (i.e. β-lactamase), decreased multiplication rate of organisms that interfere with the activity of bacteriostatic agents and reduction in pH and oxygen partial pressure, which reduces the efficacy of some antimicrobial agents (e.g. aminoglycosides and fluoroquinolones) (Brook & Foote 2005).

Some antimicrobials have a narrow spectrum of activity. For example, metronidazole is only effective against most anaerobes and therefore cannot be administered as a single agent for the therapy of mixed infections, which, as stated above, sinusitis is. The low pH and
the anaerobic environment are also unfavorable for the aminoglycosides and fluoroquinolones (Brook 2006).

**Results from studies on the use of different antibiotics in treating sinusitis**

**Penicillin**
Amoxicillin therapy is considered to be the first-line of treatment for acute bacterial sinusitis (Brook 2005, Hamory et al. 1979, Mehra & Jeong 2009, Pynn & Nish 2008). Amoxicillin is relatively safe and well tolerated. Given its intrinsic activity and excellent bioavailability, amoxicillin is generally considered the most active of all oral β-lactams against streptococci, including *S. pneumoniae*. The addition of clavulanic acid to amoxicillin does preserve the activity of the agent in the presence of β-lactamases (Anon et al. 2004).

**Macrolides**
These agents are active against Gram-positive and some Gram-negative bacteria. Although they are generally considered to be bacteriostatic, they are bactericidal against autolytic species such as pneumococci (Anon et al. 2004). Macrolides exhibit better antimicrobial activity in an environment with neutral to basic pH. This physicochemical characteristic is due to the fact that at low pH macrolides become positively charged and do not readily cross biological membranes (Anon et al. 2004).

Additionally, the increasing prevalence of macrolide resistance to *S.pneumoniae* is associated with a significant likelihood of clinical failure (Dagan et al. 2000, Haye et al. 1996). Cross-resistance of *S. pneumoniae* is also common among all macrolides (Brook 2005).

**Cephalosporins**
The physicochemical properties of many oral cephalosporins make them less suitable than penicillin/amoxicillin when *S. pneumoniae* is the infecting pathogen. Cephalosporins are inherently less active than penicillin/amoxicillin against *S. pneumoniae*. First-generation cephalosporins lack sufficient efficacy against *H. influenzae* and many *S. pneumoniae* strains (Brook et al. 2005).

Third-generation cephalosporins are most effective against penicillin-resistant *Haemophilus* and *Moraxella* spp., but they are less effective against *S.pneumoniae* resistant to penicillin (Brook 2004). Furthermore, cephalosporins are actively absorbed in the
gastrointestinal tract, which limits the concentration that can be achieved, regardless of the magnitude of dose administered (Anon et al. 2004).

**Clindamycin**
Clindamycin has good efficacy against aerobic Gram-positive organisms. It is not however, active against *H. influenzae* and *M. catarrhalis* (Anon et al. 2004).

**Fluoroquinolones**
The older quinolones (i.e. ciprofloxacin, ofloxacin) are effective against *H. influenzae* and *M. catarrhalis*, but have minimal activity against *S. pneumoniae* (Brook et al. 2005). The newer quinolones (e.g. moxifloxacin, levofloxacin) have improved activity against *S. pneumoniae* (Brook et al. 2005).

The predominant concern surrounding fluoroquinolone use pertains to the selection of class resistance in organisms such as Gram-negatives, staphylococci and pneumococci (Anon et al. 2004). As with most agents, development of resistance among *S. pneumoniae* strains to one fluoroquinolone generally leads to cross-resistance to all members of the fluoroquinolone class, and there is evidence that inappropriate use is linked to the development of resistance and to clinical failures (Kays et al. 2002, Kuehnert et al. 1999, Ross et al. 2002, Urban et al. 2001). Because of this, fluoroquinolones should not be used indiscriminately (Anon et al. 2004). These agents are currently not recommended for use in children either, because of the potential adverse effects on the cartilage (Brook et al. 2005).

**Are dentists supposed to treat patients with sinusitis?**
Sinusitis is a relatively common disease. Even so, sinus infections are among the most frequently misdiagnosed and misunderstood diseases in clinical practice. The dental clinician must be aware of the various diseases of the sinuses and their possible presentations. In the dental office, both acute and chronic sinusitis of non-odontogenic origin may present as chronic orofacial pain or atypical pain from dental origin, and will require appropriate medical referral. To determine appropriate care for a patient presenting with sinusitis symptoms, the dental clinician must understand the anatomy, pathophysiology and microbiology of the sinuses (Pynn & Nish 2008) and be able to diagnose the condition correctly.
Conclusion
Antimicrobials used for chronic sinusitis therapy should be effective against both aerobic and anaerobic microorganisms. But, controversies exist regarding the need to provide coverage against all bacterial isolates as some studies of the treatment of acute maxillary sinusitis suggested that utilization of narrow spectrum antimicrobials were as effective as wide spectrum ones (Lindbaek et al. 2004, Lindbaek et al. 2007).

Recent studies of acute sinusitis have also questioned the value of antibiotic treatment, reporting little improvement in symptom resolution when comparing antibiotics versus placebo (Merenstein et al. 2005, Williamson et al. 2007, Young et al. 2008). Most patients with acute sinusitis improve within 2 weeks without antibiotics. The potential risk of adverse effects from antibiotics may also outweigh the benefits of therapy (Baily et al. 2009).

However, patients that do receive antibiotic because of signs of systemic involvement must be monitored carefully with respect to efficacy of the agent and improvement of the symptoms. The current recommended duration of treatment when treating acute sinusitis is 10-14 days. Failure to respond to antimicrobial therapy after 3 days should prompt either a switch to alternative antimicrobial therapy or reevaluation of the patient (Anon et al. 2004). The length of therapy when treating chronic sinusitis is at least 21 days, and may be extended up to 3 month. In addition to medical therapy, surgical drainage must be considered when dealing with chronic sinusitis (Brook 2009).

The dental clinician’s job is to diagnose the condition correctly and refer the patient to his/her physician immediately.

5. Antimicrobial therapy and tonsillitis

Tonsillitis is an inflammation of the tonsils most commonly caused by viral or bacterial infection (Brook 2003, Brook 2005).

Microbiology of tonsillitis
Tonsillitis is most often polymicrobial (Kilty & Desrosiers 2008, Rajasou et al. 1996). Common bacterial pathogens include Group A beta-hemolytic streptococci and other streptococci (Brook 2003). Tonsillitis may result from infection with bacteria or viruses. Viral causes include adenovirus, infectious mononucleosis from Epstein-Barr virus infection, cytomegalovirus, HIV, hepatitis A, and rubella (Georgalas et al. 2009, Wyndham 2008).
Dias et al. (2009) conducted a study where the purpose was to characterize the association between Epstein-Barr virus and recurrent tonsillitis. The results showed that children’s tonsils can be colonized by EBV and such colonies may be associated with the pathogenesis of recurrent tonsillitis (Dias et al. 2009).

Clinical presentation
Common symptoms are sore throat and difficulty with swallowing (Wyndham 2008). Other accompanying symptoms include fever, red and/or swollen tonsils, white or yellow areas on the tonsils, halitosis, stiff neck, lymphadenopathy, cough, and headaches (Brook 2003, Wyndham 2008).

The role of antimicrobial therapy in the treatment of tonsillitis
Bacterial tonsillitis is treatable with antibiotics. Antimicrobial therapy is considered if there are signs of systemic involvement, such as fever, lymphadenopathy, and difficulty in swallowing. Tonsillectomy is considered for those who have 5 or more episodes in a year (Wyndham 2008).

The main purpose of treating acute tonsillitis cases with antibiotics is to reduce the possibility of suppurative and non-suppurative complications associated with Group A beta-hemolytic streptococci (Sih & Bricks 2008).

Results from studies on the use of different antibiotics in treating tonsillitis

Penicillin
Even though antibiotics other than penicillin are more effective in the cure of Group A beta-hemolytic streptococci tonsillitis, penicillin is still recommended in some guidelines as the antibiotics of choice (Brook 2001, Brook 2007). But, the growing inability of penicillin to eradicate Group A beta-hemolytic streptococci (GABHS) which leads to clinical and bacteriological failures is an important clinical problem (Brook 2009), and should be taken into consideration.

Various theories explain this penicillin failure that may lead to recurrent tonsillitis (Brook 1984). These explanations include bacterial interactions between GABHS and members of the tonsillar microflora. One theory is that β-lactamase producing bacteria can shield GABHS by inactivating penicillin (Brook 2005).
Another explanation is that interfering organisms such as alpha-streptococci that are part of the normal oral flora, are missing in many of those patients who fail penicillin therapy (Crowe et al. 1973, Sanders 1969, Sanders et al. 1976, 1977). These alpha-streptococci play an important protective role in preventing colonization and subsequent infection by Group A beta-hemolytic streptococci, and their absence may lead to failure of penicillin therapy (Sanders et al. 1969).

Several studies have shown that alpha-streptococci can inhibit the colonization of a variety of pathogens such as *S. pneumoniae*, GABHS, and *S. aureus* in patients as well as *in vitro* (Aly et al. 1974, Crowe et al. 1973, Johanson et al. 1970, Sanders 1969). Their production of bacteriocin and other inhibitory substances may explain this phenomenon.

Suppression of some bacterial growth may also occur through utilization of nutrients in the nasopharyngeal environment essential for the colonization by potential pathogens (Roos et al. 1989).

Eradication failure might be due to the lack of sufficient antibiotic concentration at the site of infection during the recommended treatment time. Some studies identified this phenomenon as a possible mechanism of phenoxymethylpenicillin treatment failures (Holm & Ekedahl 1982, Kaplan et al. 1974, Roos et al. 1986, Stjernquist et al. 1993, Strömberg et al. 1987, Sundberg et al. 1982).

Patients who fail penicillin therapy may respond to treatment effective against beta-lactamase producing bacteria, such as amoxicillin-clavulanate (Pichichero & Casey 2007).

**Cephalosporins**

The success rate of eradication of Group A beta-hemolytic streptococci in acute tonsillitis is higher with cephalosporins than with penicillins (Brook 2005, Casey et al. 2004). The cephalosporins increased efficacy may be due to their activity against aerobic β-lactamase producing bacterial such as *S. aureus, Haemophilus* spp. and *M. catarrhalis*.

Another possible reason is that the non-pathogenic interfering aerobic and anaerobic bacteria which compete with GABHS (Brook 2005), are more resistant to cephalosporins than to penicillin and are therefore more likely to survive cephalosporin therapy (Brook 2004).
Macrolides

Macrolides are also an alternative choice therapy of tonsillitis (Brook 2009). O’Doherty et al. (1996) compared the efficacy and safety of azithromycin and penicillin V in the treatment of acute streptococcal pharyngitis/tonsillitis in pediatric patients. A total of 489 children were randomized into 3 test-groups: (1) Penicillin V 125-250 mg 4 x daily for 10 days, (2) Azithromycin 10 mg/kg 1 x daily for 3 days, (3) Azithromycin 20 mg/kg 1 x daily for 3 days. A satisfactory clinical response was recorded in all 3 test-groups. The authors concluded that azithromycin was as safe and effective as penicillin V in the treatment of acute pharyngitis/tonsillitis.

However, their increased use has been associated with increased Group A beta-hemolytic streptococci resistance (Urbanek et al. 2004). Resistance of Group A beta-hemolytic streptococci to macrolides reached up to 70% in Finland, Italy, Japan and Turkey (Colakoglu et al. 2006). In the United States, the current resistance is 6-16% (Richter et al. 2005). Clinicians therefore advise to avoid the routine use of macrolides for Group A beta-hemolytic streptococci tonsillitis and reserve them for those with penicillin allergy (Brook 2009).

Metronidazole

Therapy with metronidazole relieved the symptoms of tonsillar hypertrophy and shortened the duration of fever in patients with infectious mononucleosis (Hedström et al. 1978). Because metronidazole has no antiviral or anaerobic bacterial activity, suppression of the oral anaerobic flora may explain its clinical effects. It has been suggested that this microflora may act synergistically with the Epstein-Barr virus (Hedström et al. 1978). This explanation is supported by the increased recovery of P. intermedia and F. nucleatum during the acute phases of infectious mononucleosis (Brook 1992).

Fluoroquinolones

There are very few studies were the tonsillar tissue concentration of fluoroquinolones has been investigated. In one such study, the moxifloxacin concentration in plasma and tonsillar tissue was determined (Esposito et al. 2006). The authors concluded that moxifloxacin achieves good penetration in tonsillar tissue, but long-term follow-up data on these agents are not yet available.
Conclusion
Taking into account the difficulty of penicillin to penetrate the tonsillar tissue, the increasing macrolide resistance among streptococcal strains, and the changing epidemiology of pharyngotonsillitis etiology, it is clear that the management of tonsillitis is challenging.

Overuse and inappropriate use of antibiotics has led to the emergence of bacterial resistance, in addition to exposure to unnecessary side effects (Ayyad et al. 2009). Additionally, misuse of antibiotic therapy and thereby changes to the tonsillar microflora, and viral infections have also been listed as predisposing factors for recurrent tonsillitis (Dias et al. 2009).

The dental clinician must be aware of the various signs and symptoms of tonsillitis, in order to be able to determine appropriate care for a patient presenting with tonsillitis symptoms. Diagnosis of acute tonsillitis is primarily clinical, with the main interest being whether the illness is viral or bacterial - this being of relevance if antibiotics are being considered (Georgalas et al. 2009). Studies have attempted to distinguish viral from bacterial tonsillitis on clinical grounds, but the results are conflicting, suggesting a lack of reliable diagnostic criteria. It has been estimated that 75 % of tonsillitis cases in children are caused by viruses; however, most of these cases are treated with antibiotics (Bricks 2003, Del Mar et al. 2006, Sih & Bricks 2008).

Antimicrobial therapy must be considered only if there are signs of systemic involvement, such as fever, lymphadenopathy, and difficulty in swallowing. The condition must be correctly diagnosed, and the patient must be referred to his/her physician immediately.

6. Antimicrobial therapy and sialadenitis

What is sialadenitis?
Sialadenitis is an infection of the salivary glands (Sialadenitis 2011). It can occur in any of the glands, and can present as an acute single episode or as multiple recurrent episodes (Brook 2009, Sialadenitis 2011). The parotid gland is the salivary gland most commonly affected by inflammation (Brook 2007). The parotid gland is almost purely a serous gland and is therefore highly susceptible to infection secondary to stasis. In contrast, the increased mucus concentration within sublingual and submandibular gland gives bacteriostatic protection (Magilner & Amburgey 2008).
Clinical features of sialadenitis are typically an enlarged, tender or a red salivary gland (Sialadenitis 2011). Other symptoms may be difficulty in opening the mouth, fever, or swelling of the lymph nodes in the neck region (Sialadenitis 2011, What is Sialadenitis? 2011).

Sialadenitis may be classified as acute or chronic, and may be bacterial, viral, fungal, mycobacterial or parasitic (Carlson 2009). An acute sialadenitis may be diagnosed when symptoms have existed less than 1 month, while a chronic condition is considered when symptoms are greater than 1 month in duration (Carlson 2009, Mandel & Witek 2001, Patel & Karlis 2009, Yu et al. 2007).

The dental clinician has to be aware that a chronic sialadenitis most often is secondary to sialolithiasis. Sialolithiasis is the formation of stones in a salivary gland or duct (Primehealthchannel 2011). Diagnosis of salivary gland stones are done by medical history and physical examination. Common sialolithiasis symptoms include swelling and discomfort in the affected salivary gland. Since chewing promotes release of saliva, symptoms tend to exacerbate during meals. Confirmation of sialolithiasis can be done by X-rays (Intelligentdental 2011).

**Microbiology sialadenitis**

Viruses are the most common causes of parotitis in children (Brook 2003, Brook 2007, Brook 2009), including paramyxovirus (mumps), HIV, Epstein-Barr virus, coxsackievirus, parainfluenza virus, influenza virus, and cytomegalovirus (Brook 2003).


**Clinical presentation**

Acute suppurative parotitis occurs mostly in children younger than 2 months of age and in elderly patients who are debilitated by systemic illness; although persons of all ages may be affected (Brook 1992, Krippaehne et al. 1962). Other predisposing factors include dehydration, immunosuppression, malnutrition, poor oral hygiene, trauma, neoplasms of the oral cavity, ductal obstruction and medications that diminish salivary flow (Echevvarria et al. 1987, Fordyce & Stassen 1996, Krippaehne et al. 1962). It is evident that the clinician should,
if possible, reverse such conditions during the acute phase of the sialadenitis to prevent spread of infection or the development of a chronic sialadenitis (Carlson 2009). Correct diagnose is crucial, and the dental clinician need to refer the patient to his/her physician as soon as possible, to avoid Doctor’s delay.

The role of antimicrobial therapy in the treatment of sialadenitis
As mentioned above, the initial evaluation of a patient with a salivary gland swelling must begin with a comprehensive history and examination. Therapy includes maintenance of hydration and administration of oral or parenteral antimicrobials. Once an abscess has formed, drainage is required.

Maintenance of good oral hygiene, adequate hydration and early and proper therapy of bacterial infection is crucial (Antoniades & Harrison 2004, Brook 2007).

The choice of antibiotic depends on the etiologic agent. Most patients respond to antimicrobial therapy; however, some inflamed glands may reach a stage of abscess formation that requires surgical drainage immediately (Brook 2007). In bacterial sialadenitis, antibiotic selection should reflect the fact that \textit{S.aureus} is frequently cultured in cases of acute supplicative parotitis. The patient needs to be monitored carefully. For cases which do not respond over 3 days, an antibiotic change should be considered.

Broad antimicrobial coverage is indicated to cover all possible aerobic and anaerobic pathogens, including adequate coverage for \textit{S. aureus}, GABHS, and β-lactamase producing bacteria (Brook 2007). Clearly, the greater the magnitude of purulent infection noted on physical examination, the greater the likelihood that admission to the hospital and incision and drainage will be necessary (Carlson 2009).

When it comes to chronic sialadenitis, antibiotics have been used in treating the exacerbations that are so characteristic of the disease. They are effective in controlling the acute attack; but are unable to heal the disease or to prevent further recurrent infections (Diamant & Enfors 1965). This is because the obstruction of the duct in chronic sialadenitis is most often caused by sialolithiasis. Therefore, in chronic recurrent sialadenitis, usually surgery is considered (Diamant & Enfors 1965, Brook 2003, Brook 2005, Katz et al. 2009), and the patient needs to be referred immediately.
7. Special topics

7.1 Endocarditis prophylaxis

Bacterial endocarditis is an infection of either the heart’s inner lining (endocardium) or the heart valves (Endocarditis 2011). The term prophylactic antibiotic implies the use of antimicrobial agents to prevent infections (Abubaker et al. 2009, Pallasch 2003). Surgical procedures in the oral cavity are particularly liable to contamination with the local flora found there (Alfter et al. 1995).

The most common cause of this infection is bacteria (Ito 2006), and *Streptococcus viridans* has been implicated as the most common cause of infective endocarditis (Chopra & Kaatz 2010, Maestre et al. 2006, Hills-Smith & Schuman 1983, Endocarditis 2011). The antibiotic chosen must therefore target this microorganism.

The rationale for the use of infective endocarditis prophylaxis is based on the concept that if bacteremia, which is a crucial component of the pathogenesis of infective endocarditis, is prevented, the sequence of events that lead to formation of a vegetation on previously damaged valves can be prevented (Chopra & Kaatz 2010). Infective endocarditis is a life threatening disease, and prevention is always better to avoid dreadful complications or death (Dhoble et al. 2009).

When endocarditis prophylaxis is indicated, one should seek the help of current treatment guidelines. These guidelines include the American Heart Association (AHA), the British Society for Antimicrobial Chemotherapy (BSAC) and the European Society of Cardiology (ESC) guidelines. The British Society for Antimicrobial Chemotherapy (BSAC) recommends 3 g amoxicillin in adults 1 hour before treatment, and in case of penicillin allergy, clindamycin 600 mg 1 hour before dental treatment (Gould et al. 2006). The American Heart Association (AHA) (Ebmil & Chan 2008, Taubert & Dajani 1998) and the European Society of Cardiology (ESC) (Gutiérrez et al. 2006, Habib et al. 2009), recommends a single dose of 2 g amoxicillin in adults 1 hour before dental treatment. If the patients has penicillin allergy, 600 mg clindamycin 1 hour before dental treatment is recommended (Habib et al. 2009, Taubert & Dajani 1998).

Recommended dosage for children is amoxicillin 50 mg/kg (maximum 2 g) 1 hour before dental treatment and for children with penicillin allergy clindamycin 20 mg/kg (maximum 600 mg) 1 hour before dental treatment (Hills-Smith & Schuman 1983, Planells del Pozo et al. 2006).
The Norwegian recommendations on endocarditis prophylaxis in dental practice currently follow these guidelines from AHA and ESC (Aakhus & Bjørneklett 2008). It is therefore important that the dental practitioner follows the recommendations from AHA and ESC, and keep up to date on new recommendations when old ones are revised (Taubert & Dajani 1998).

7.2 Antimicrobial agent and drug interactions

A drug interaction is a situation in which a substance affects the activity of another substance (Drug interaction 2011). Generally speaking, drug interactions should be avoided. However, drug interactions have also been deliberately used, such as co-administering probenecid with penicillin (probenecid inhibits the excretion of penicillin, and therefore penicillin persists longer when taken simultaneously with probenecid) (Rang & Dale 2007, Drug interaction 2011).

Also, combination therapy with two antibiotics is used in special cases to take advantage of antibiotic synergism. Antibiotic synergism occurs when the effects of a combination of antibiotics is greater than the sum of the effects of the individual antibiotics, such as trimethoprim-sulfamethoxazole (Rang & Dale 2007, Drug interaction 2011).

Interaction of antibiotics with medicament substrates of the cytochrome family

The enzymatic systems involved in the bio-transformation of the majority of the medicaments are located in the inner membrane of mitochondria or in the smooth endoplasmatic reticulum of the liver, which contains an important group of oxidative enzymes (Cytochrome P450 2011). This is the location of the cytochrome family of which the P450 cytochrome system is prominent (Rang & Dale 2007, Stockley 2002). The CYP3A4 isoform is the most abundant cytochrome family in the liver and human intestine. In pharmacological interactions an induction or enzymatic inhibition can be produced at the metabolic level (Cytochrome P450).

The macrolide antibiotics erythromycin and clarithromycin are potent irreversible inhibitors of the CYP3A4 and CYP1A2 isoenzymes, which can significantly increase concentrations in blood and toxicity of other medicaments which use this system of detoxification (Felleskatalogen 2011, Hersh & Moore 2008). Azithromycin is also a macrolide drug. However, this agent is not an inhibitor of the mentioned isoenzymes, which makes it a safe alternative in patients who have penicillin allergy and are taking other medicaments which could cause problems with erythromycin or clarithromycin (Felleskatalogen 2011, Gomez-Moreno et al. 2009).
Ciprofloxacin and erythromycin are inhibitors of the CYP1A2 isoenzymes, which can reduce biotransformation and increase blood levels of medicaments which are substrates of CYP1A2 such as antihistamines (teofilin), antidepressors (imipramine) and tacrine (Felleskatalogen 2011, Hersh & Moore 2008, Stockley 2002, Macrolides 2011, Quinolone 2011).

Metronidazole inhibits CYP2C9, and will give rise to an accumulation of various substrates of this isoenzyme (Gomez-Moreno et al. 2009). The CYP2C9 substrates include anticoagulants (warfarin), anticonvulsives (fenitoin) and NSAIDs (ibuprofen, naproxen, diclofen) (Hersh 1999, Hersh & Moore 2008, Sims & Sims 2007).

It is advisable that before prescribing metronidazole to patients undergoing long-term treatment with warfarin to consult with the patients physician. As mentioned above; since metronidazole is generally used for the anaerobic component of oral infections together with penicillin which treats the aerobic, other antibiotics can be used as an alternative for these mixed infections, such as clindamycin (Gomez-Moreno et al. 2009).

Interaction of metronidazole with alcohol
Metronidazole inhibits the activity of the enzyme acetaldehyde dehydrogenase leading to an accumulation of acetaldehyde in patients consuming alcohol (Gupta et al. 1970). The reaction leads to nauseas, cardiac palpitations and headache (Felleskatalogen 2011). The dentist should warn the patients not to drink alcohol during metronidazole treatment for at least 3 days after the final treatment (Felleskatalogen 2011, Hersh & Moore 2004).

Interaction of tetracyclines with cations
Tetracyclines form chelates with polyvalent cations found in the diet, antacids and vitamins (Norsk Legemiddelhåndbok 2005). These chelates are insoluble and cannot be absorbed through the gastrointestinal tract mucosa and the blood stream and so are excreted (Gomez-Moreno et al. 2009, Kampmann et al. 2007). Polyvalent cations include calcium, magnesium, bismuth, iron, zinc and aluminum (Felleskatalogen 2011, Gomez-Moreno et al. 2009).

In these cases it would be prudent that the dentist advise the patient to avoid simultaneous ingestion of tetracycline and polyvalent cations (Gomez-Moreno et al. 2009).

Interaction of antibiotics with oral anticoagulants
Generally, antibiotics alter the normal intestinal flora, especially those that are broad-spectrum. This flora is important in preventing overgrowth of opportunistic infections in the
gastrointestinal tract and is essential for the production and/or absorption of some nutrients, vitamins and medicaments (Kampmann et al. 2007, Rang & Dale 2007). Intake of antibiotics can lead to less absorption of vitamin K and consequently coagulation factors, VII, IX, and X (Sims & Sims 2007). Therefore there is a greater risk of bleeding which is clinically important in patients undergoing warfarin treatment over prolonged periods (Gomez-Moreno et al. 2009).

Interaction of antibiotics with oral contraceptives
The two components of contraceptive pills, semi-synthetic estrogens and semi-synthetic progesterones are CYP3A4 substrates (Hersh & Moore 2008, Stockley 2002). It has been shown that rifampicin significantly reduces blood levels of the contraceptive as they are potent inducers of the CYP3A4 isoform (Kampmann et al. 2007). Therefore, the dentist should warn woman using contraceptives of the possible interaction when prescribing antibiotics (Gomez-Moreno et al. 2009).

Interaction of bacteriostatic antibiotics with bactericidal antimicrobial agents
Since some antimicrobial agents work by interfering with DNA synthesis, it is logical that the drugs that are bactericidal would be less effective in a culture whose growth is arrested by a bacteriostatic agent. Therefore, it is suggested that bactericidal and bacteriostatic antibiotics should not be combined (Gomez-Moreno et al. 2009).

8. Concluding remarks
The use of antibiotics in dentistry is diverse, and only a selected number of articles on this subject have been discussed in this paper. However, despite the great variety of antibiotics, some important principles can be summarized from the articles discussed:

- Patient evaluation should start with a thorough history and examination
- Antibiotic treatment should be started only if clear indications exist
- Right diagnosis is crucial for the selection of an appropriate therapy
- The treatment chosen must be assessed as beneficial for the patient
- Allergic and toxic reactions must be regarded
- The potential risk of adverse effects from antibiotics must be weighed against the benefits of therapy
- The selection of antimicrobial agents should be guided by their aerobic and anaerobic antibacterial spectrum
- Resistance patterns of the pathogens involved in the infection must be taken into account

The selection of antimicrobial agents is simplified when reliable culture results are available. However, this may not always be possible because of difficulty obtaining appropriate specimens, and the fact that the patient may need emergency treatment. Therefore, many patients are treated empirically on the basis of suspected pathogens.

Fortunately, the types of microorganisms involved in most odontogenic infections and their antimicrobial susceptibility patterns tend to be predictable, although they may vary in particular settings. Therefore, it is important that the clinician has knowledge about what type of organisms to expect in any type of odontogenic infection, in order to be able to make the correct decision about what therapy and/or antibiotic agent to choose.

The choice of antibacterial agents is also influenced by factors other than susceptibility patterns. These include the pharmacokinetic and pharmacodynamic characteristics of the various drugs, their toxicity, effect on the normal flora, and bacteriostatic/bactericidal activity.

The emergence of resistant microorganisms against antibiotics is directly related with the excessive use of these drugs (Arnold et al. 2005, Arroll et al. 2005, Moloney & Stassen 2009). Antibiotic resistance in oral microbes is an issue of concern in general dental practice where antibiotics are, in some cases, essential (Al-Haroni et al. 2008, Harrison et al. 1985). Antibiotic therapy can also affect the balance between pathogens and normal flora by disturbing the ecological balance thus facilitating recurrent odontogenic infections.

It has therefore never been more important for us to understand in detail the mechanisms of and routes to resistance in pathogenic bacteria, so that we can adjust our clinical behavior in ways that minimize the future growth of resistance (Rice 2009).

Therefore, it is important that the dental clinician keep pace with new knowledge concomitantly with maintenance of basic comprehension.

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