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Antibiotics in the treatment of peri-implantitis

Key words antibiotics, peri-implantitis, review

Purpose: To review and discuss current literature on the use of systemically administered or locally delivered antibiotics in the treatment of peri-implantitis.

Materials and methods: A literature search was conducted using MEDLINE through the PubMed database of the US National Library of Medicine using studies up to 2011. Studies on the microbiology of peri-implantitis lesions were hand selected.

Results and conclusions: Two studies on the use of systemically administered antibiotics in the treatment of peri-implantitis were identified. Both studies involved a case series without controls. Five studies on locally delivered antibiotics were found. In all cases, local antibiotics were used in conjunction with mechanical debridement and chemical disinfection with antimicrobial agents such as chlorhexidine digluconate or hydrogen peroxide. The additional effects of local antibiotics were noted in all studies but were in general moderate. This may in part be due to the selection of patients with advanced deep pockets and advanced bone loss. The current available scientific information on the use of locally or systemically administered antibiotics is insufficient to allow any firm specific recommendations for the use of these drugs. Local application of minocycline or doxycycline as an adjunct to mechanical debridement and irrigation with an antimicrobial agent may be effective in moderately deep lesions. Surgical access by full-thickness flap surgery in deeper lesions is probably necessary to halt the progression of bone loss. No sound scientific basis is available for the use of systemic antibiotics. There is an urgent need for randomised clinical trials on the use of antibiotics in the treatment of peri-implantitis. Proper periodontal infection control in dentate patients before implants are installed and frequent supportive implant care represent effective measures to reduce the risk of future infections and their complications around oral implants.

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Introduction

Oral implants have become a reliable alternative to replace lost teeth. They support dental prostheses, crowns and bridges to restore oral function and aesthetics. As successful as they have been, implant complications and losses do occur. Usually these failures are categorised as early or late failures. Infection can play a role in both events. Biological complications of oral implants involve abscess or
fistula formation and alveolar bone loss due to chronic peri-implant infection (peri-implantitis). Inflammation of the peri-implant soft tissues without bone loss is referred to as mucositis. The condition of inflammation of peri-implant tissues involving loss of supporting bone is referred to as peri-implantitis. Mucositis occurs in the majority of patients with oral endosseous implants (80%) and around approximately 50% of those implants. The prevalence of peri-implantitis has been poorly studied but is estimated to range from 28% to >50% of subjects and from 12% to 43% of the implant sites. This variance may be explained by lack of a proper definition of the threshold.

Established risk factors for peri-implantitis are poor oral hygiene, a history of periodontitis and smoking. Other factors such as poor metabolic control of diabetes, alcohol consumption, genetic traits and implant surface characteristics may also increase the risk of peri-implantitis.

The rationale of mucositis and peri-implantitis treatment is based on the notion that biofilm formation plays an essential role in the aetiology of these infections. Therefore, treatment of peri-implant infections is cause related and aims to reduce the total peri-implant bacterial load.

Mucositis is a reversible inflammatory disorder, and tissue debridement and surface decontamination of implant structures have shown to be effective in restoring peri-implant tissue health. Adjunctive chemical antimicrobial mouth rinses enhance mechanical debridement procedures. In contrast, mechanical non-surgical treatment of peri-implantitis lesions has shown unpredictable and little effect on clinical outcome parameters such as bleeding on probing, probing depth reduction and bone level. Other approaches to control implant biofilms such as laser therapy and photodynamic therapy have shown moderate to little effects on peri-implantitis lesions.

Locally and systemically delivered antibiotics as adjuncts to mechanical debridement have shown clinical benefits in the treatment of periodontitis. The use of antibiotics has also been applied in peri-implantitis treatment. The aim of this study is to summarise the microbiology of peri-implant lesions and to evaluate the clinical results of locally or systemically delivered antibiotics in the (adjunctive) treatment of peri-implantitis.

### Materials and methods

A literature search was conducted using MEDLINE (through the PubMed database of the US National Library of Medicine) including studies published up to 2011. Key words included in this search were: ‘peri-implantitis’, ‘treatment peri-implantitis’, ‘antibiotic treatment peri-implantitis’, ‘antimicrobial therapy peri-implantitis’, ‘antimicrobial therapy peri-implantitis’ and ‘local delivery peri-implantitis’.

Studies on the microbiology of peri-implantitis lesions were hand selected. Case studies, non-English papers and animal studies were not included in this review.

### Results

#### Microbiology of peri-implantitis lesions

Different methods have been used to study the microbial composition of peri-implantitis lesions including differential phase-contrast microscopic analysis to study the relative distribution of different bacterial morphotypes, culturing, latex agglutination test, checkerboard DNA-DNA hybridisation, or polymerase chain reaction. Only one study identified both different morphotypes and specific bacteria. The composition of the submucosal biofilm in the sulci around healthy implants is very similar to the microflora of healthy shallow periodontal sulci. The composition of the submucosal biofilm in peri-implantitis lesions resembles the subgingival biofilm in chronic periodontitis with high proportions of motile rods and spirochetes, Porphyromonas gingivalis, Tannerella forsythia, Fusobacterium spp, Treponema species and Prevotella intermedia. Using checkerboard DNA-DNA hybridisation it was found that Prevotella nigrescens, Parvimonas (Peptostreptococcus) micra and Fusobacterium nucleatum were positively associated with peri-implantitis lesions in comparison to healthy control sites. A trend for higher prevalence was found for P. gingivalis, T. forsythia and Treponema denticola. Others have reported high prevalence of specific pathogens such Aggregatibacter actinomycetemcomitans or T. forsythia. Enteric rods, staphylococci and yeasts have
been isolated infrequently from deep peri-implant bone defects.\textsuperscript{23,24}

The composition of the submucosal biofilm in peri-implantitis lesions in dentate subjects may differ in comparison to lesions in fully edentulous subjects. More black pigmented Gram negative anaerobic species were found in samples from partially edentulous patients than in samples from fully edentulous patients.\textsuperscript{17} Mombelli et al\textsuperscript{18} using culture technique, found no \textit{P. gingivalis} in peri-implantitis lesions in healthy implant sites in edentulous subjects. Colonisation of the peri-implant sulcus seems to occur rapidly. Koka et al\textsuperscript{25} found \textit{P. gingivalis}, \textit{P. intermedia} and \textit{F. nucleatum} 14 to 28 days after exposure of implant surfaces to the oral environment in partially edentulous subjects. \textit{A. actinomycetemcomitans} was not found 6 months after loading of the implants.\textsuperscript{26} No differences were observed in the prevalence of various periodontal species in the subgingival plaque from teeth and implants 6 months after abutment connection, and this did not change over a period of 3 years.\textsuperscript{24} Also, the use of different types of abutments (zirconia or titanium) did not result in differences in early bacterial colonisation.\textsuperscript{27}

It has been suggested that the periodontal pathogens \textit{A. actinomycetemcomitans} and \textit{P. gingivalis} are no longer detectable on oral mucous surfaces after edentulation.\textsuperscript{28} However, \textit{P. gingivalis} may survive in some edentulous individuals wearing full prostheses.\textsuperscript{29} This observation has been confirmed by several other studies.\textsuperscript{30,31} Karbach et al\textsuperscript{15} found that the percentage of implants with periodontal pathogens was significantly lower in fully edentulous patients than in partially edentulous patients ($P = 0.037$). This is consistent with the finding of Kocar et al\textsuperscript{16} who found that the presence of \textit{A. actinomycetemcomitans}, \textit{P. gingivalis}, \textit{T. forsythia}, and \textit{T. denticola} was common in healthy peri-implant sulci of partially edentulous patients but that these species were virtually absent in the peri-implant sulci of completely edentulous patients.

In conclusion, the submucosal biofilm in peri-implantitis lesions greatly resembles the subgingival biofilm in chronic periodontitis. However, as in periodontitis, the composition of the peri-implantitis biofilm may differ among different patient categories and may depend on the presence of natural teeth and the periodontal history and periodontal condition of the patient. More information is needed on the prevalence and the role of unusual pathogens such as staphylococci, enteric rods and yeasts.

**Antibiotics in peri-implantitis**

No clinical study is available on the effects of antibiotics as the sole therapy in the treatment of peri-implantitis. In all clinical trials, administration of antibiotics is always combined with either non-surgical or surgical interventions without a proper control group. There is also no placebo-controlled, double-blind randomised clinical trial available to show the clinical effects of a systemic antibiotic therapy as an adjunct to non-surgical or surgical treatment of peri-implantitis. This leaves the question open as to what extent antibiotics, either delivered systemically or locally, add to the clinical outcome of the treatment.

**Systemic antibiotics in non-surgical treatment of peri-implantitis**

There is one, uncontrolled study available in the literature that documents the clinical and microbiological effects of non-surgical treatment of peri-implantitis in conjunction with a systemic antimicrobial therapy.\textsuperscript{32} The patients selected for the study were partially or fully edentulous and showed ‘marked bone loss’ and probing depths of >5 mm. In order to be treated with antibiotics, submucosal samples from deep lesions needed to contain $>10^6$ CFU/ml and $>20\%$ of Gram negative anaerobic bacteria. The treatment of the peri-implantitis lesions included mechanical debridement of all accessible surfaces, irrigation of all peri-implant pockets with 0.5% chlorhexidine, systemic administration of ornidazole (1000 mg daily for 10 days) and self-performed irrigation of all deep pockets during the 10 days of systemic antibiotic therapy. Of the 11 selected patients, 9 completed the 12-month study. The authors do not describe the recall frequency of these patients. The overall clinical effect of the intervention was a significant reduction of probing depth, bleeding on probing (Table 1) and a marked suppression of the anaerobic microflora during the 12 months of monitoring. In some lesions, bone fill was noted. The study showed that the combination of local debridement and disinfection in combination with a systemic antimicrobial therapy...
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can improve clinical parameters of peri-implantitis lesions and that these changes can be maintained for at least a year. From this study, it is not possible to conclude that systemic antimicrobials are effective in the control of peri-implantitis. Indeed several antimicrobial measures were included and no control group was available.

### Antibiotics in surgical treatment of peri-implantitis

At present there is only one study available that describes the effects of surgical intervention and systemic antimicrobial therapy in subjects with peri-implantitis. The study is a case series of 9 partially edentulous subjects with 44 implants of which 26 (59%) showed bone loss, bleeding on probing and/or suppuration from the peri-implant sulci. All patients had been treated for advanced periodontitis. The intervention included surgical exposure of the implants with peri-implantitis, local cleaning with 10% hydrogen peroxide, removal of granulation tissue and abutments were sterilised and replaced.

Following surgery, the patients rinsed with 0.2% chlorhexidine digluconate for 14 days. In the 9 patients involved in the trial, a total of six different antibiotic regimens were used based on the microbiological composition of the peri-implant biofilm at baseline. During the 5 years of maintenance, retreatment with the same combination of surgical treatment and antibiotics was performed when further marginal bone loss was noted. After 5 years, 7 out of 26 implants were lost (27%), 4 out of 26 showed continuing bone loss, 9 out of 26 implants showed an unchanged bone level and 6 out of 26 implant sites showed bone gain. The authors concluded that the treatment was successful in 58% of the implants. Since there was no control group, it is not possible to determine the additional effects of the various systemic antibiotic regimens.

### Locally delivered antibiotics

Five studies on the use of locally delivered antibiotics in the treatment of peri-implantitis were identified. Two studies describe the same patient population and treatment. The original study was used for this review.

Theoretical advantages of locally administered antibiotics in comparison to systemically delivered antibiotics are:

- the high concentrations that can be achieved
- the significantly reduced risk for side and adverse effects
- the absence of interaction with other drugs
- the reduced risk of the emergence of antibiotic-resistant bacteria
- the independence from patient compliance due to the professional delivery of the drug.

In all studies describing the clinical effects of locally delivered antibiotics, the antimicrobials were used in combination with non-surgical treatment. The lat-

<table>
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<th>Table 1</th>
<th>Studies on the clinical effects of systemic antibiotics in the treatment of peri-implantitis.</th>
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<td><strong>Author</strong></td>
<td><strong>Patients and implants</strong></td>
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<tr>
<td>Mombelli and Lang (case series)</td>
<td>9 subjects, 9 implants</td>
</tr>
<tr>
<td>Leonhardt et al</td>
<td>9 partially dentate subjects, 44 implants</td>
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PPD: probing pocket depth; BoP: bleeding on probing; CHX: chlorhexidine; mBI: modified bleeding index
ter treatment consisted of mechanical debridement and cleaning of all implant structures, and chemical disinfection with antimicrobials such as chlorhexidine or hydrogen peroxide. Submucosal irrigation with chlorhexidine has also been applied as an adjunct in some studies (Table 2).

The antibiotics that have been tested in the control of peri-implantitis all belong to the group of tetracyclines. Tetracycline HCl has been developed in a system consisting of polymeric fibres (Actisite®). This system was used in the study by Mombelli et al35 and applied in partially edentulous patients with peri-implantitis lesions with a probing pocket depth (PPD) of >5 mm around the implants (ITI Bonefit®). At 12 months the mean PPD reduction amounted to 1.25 mm. The average PPD reduction of the deepest sites at all implants was 2.18 mm. At all time points (1, 3, 6 and 12 months), clinical improvement in terms of PPD and modified bleeding index were significantly better in comparison to baseline values. It should however be noted that the PPD change ranged from 0.75 mm to 4.0 mm. Three subjects showed continuing active disease during the experimental period and were expelled from the study. Increase in PPD (1 implant) was observed as well as no change in PPD (6 implants). The study results show that local application was effective in improving the clinical condition but not all patients/sites were responsive to the treatment.

Renvert and co-workers33 studied the effect of locally delivered minocycline in patients with minor bone loss (<3 threads over a period of 10–12 years). The antimicrobial device (Arestin®) consists of microspheres containing a total of 1 mg of minocycline hydrochloride. The 32 subjects (41–75 years of age) had all been treated with Brånemark system® implants and were evaluated after 10 to 12 years. The reduction in PPD of the sites treated with minocycline was minimal and amounted to 0.3 mm and 0.6 mm for the deepest probing sites. The mean

<table>
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<tr>
<th>Authors</th>
<th>Study design</th>
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<tr>
<td>Mombelli et al35</td>
<td>Case series</td>
<td>25 partially edentulous patients, 30 ITI Bonefit hollow cylinders</td>
<td>≥5 mm PPD, bone loss</td>
<td>Mechanical debridement of all surfaces, TTC fibres at 10 days, retreatment and rinsing with CHX at 14 days</td>
<td>Up to 12 months</td>
<td>12-month results: mean PPD reduction 1.25 mm, range -0.75–4.0 mm Reduction in BoS of 0.46, active disease in 10% of sites, no PPD reduction in 20% of deep sites CFU back to BL levels after 12 months</td>
</tr>
<tr>
<td>Renvert et al33</td>
<td>Randomised, two-arm trial</td>
<td>32 patients, dental status unknown, Brånemark implants</td>
<td>Bone loss &lt;3 threads, PPD ≥4 mm, BoP and/or pus</td>
<td>Mechanical debridement of all surfaces, local minocycline or CHX gel</td>
<td>Up to 12 months</td>
<td>Reduction in PI over 12 months  PPD reduction ranged from 0.4 to 0.6 mm BoP reduced but returned to baseline at 12 months</td>
</tr>
<tr>
<td>Salvi et al36</td>
<td>Case series</td>
<td>25 partially edentulous patients, 31 implants</td>
<td>History of periodontitis, PI ≤25%, ≤20% sites PPD ≥5 mm and BoP, marked bone loss</td>
<td>Mechanical debridement, 0.2% CHX gel, local minocycline</td>
<td>Up to 12 months</td>
<td>At 12 months: significant PPD reduction (range 1–1.7 mm), significant reduction in BoP in moderate and deep sites, significant gain in CAL (1.1–1.8 mm)</td>
</tr>
<tr>
<td>Büchter et al37</td>
<td>Randomised, single blind controlled trial</td>
<td>28 partially edentulous patients, 48 ITI (SLA Straumann) implants for 5.2 years</td>
<td>Bone loss exceeding 50% of the length of the dental implants, PPD &gt;5 mm, BoP</td>
<td>FMD, irrigation with 0.2% CHX at 2 weeks Mechanical treatment (control) or mechanical treatment plus local doxycycline (test)</td>
<td>18 weeks</td>
<td>At 18 weeks: significant reduction in BoP and CAL in doxycycline group versus controls</td>
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BoP: bleeding on probing; FMD: full mouth mechanical debridement; CHX: chlorhexidine digluconate; PI: plaque index; CAL: clinical attachment level; BoS: bleeding on sampling.
bleeding on probing score of the implant sites initially decreased from 88% to 40% at 1 month, but gradually increased at 12 months to 71%.

The case cohort study of Salvi et al\(^{36}\) also studied the clinical effects of locally delivered minocycline microspheres in peri-implantitis lesions. All 25 patients, with a total of 31 implants, received surgical and non-surgical periodontal treatment and, at baseline, showed full-mouth plaque scores ≤25% and ≤20% of residual sites with PPD ≥5 mm with bleeding on probing. The amount of bone loss is not provided and is only described as ‘marked’. Repeated application of minocycline was allowed in this study when, at day 180 or day 270, an increase in PPD of >2 mm was observed relative to the previous visit. This rescue treatment was performed at three implants (10%). Six implants (19%) in six subjects were lost during the 12-month evaluation period. Also in this study, a clear mean reduction in PPD was observed but was a moderate 1 mm over the 12-month period. The bleeding on probing reduced more than 50%, i.e. from 69 to 19 at 12 months. During the study period, the plaque scores remained very low.

Büchter et al\(^{37}\) selected 28 patients for a randomised single-blind study to examine the additional clinical effects of 8.5% doxycycline (Atridox\(^{®}\)). Patients had in total 48 ITI (SLA Straumann) implants that had been in function for a mean period of 5.2 (±2.1) years. All patients had bone defects exceeding 50% of the length of the dental implants. Periodontal treatment was given if ‘tooth replacements were the result of periodontitis’. Patients had received full-mouth debridement and subgingival irrigation of the peri-implant defect with 0.2% chlorhexidine digluconate 2 to 6 weeks before the baseline examination. After removal of the prosthetic restoration, abutments were sterilised, implant defects were repeatedly irrigated with 0.2% chlorhexidine and, after local anaesthesia, mechanical debridement of the implant was performed with plastic instruments.

In the experimental group (n = 14) mechanical debridement was followed by application of the doxycycline gel. Follow-up included weekly attendance of an oral hygiene programme and oral hygiene instruction. Treatment was assessed after 18 weeks. In both groups, mean PPD changes and mean attachment level changes were significant. The group treated with adjunct local doxycycline showed a significantly greater reduction of PPD (\(P = 0.046\)) and attachment level gain (\(P = 0.024\)) than the control group. Bleeding on probing was also only significantly reduced in the doxycycline treated group.

**Discussion**

The scientific information on the clinical efficacy of antibiotics to control peri-implantitis is far from sufficient to provide an evidence-based approach to create clinical guidelines for treating these peri-implant infections. The treatment protocols basically originate from the field of periodontology. Non-surgical treatment involves mechanical debride-ment of the implant surface and surrounding tissues with curettes, pocket irrigation with disinfectants such as chlorhexidine (0.2%) or hydrogen peroxide (3-10%), and the use of local or systemically administered antibiotics. For most systems, the surface and geometry of the implant do not allow proper removal of biofilm deposits using periodontal instru-ments. This is probably the reason that non-surgical treatment of moderate peri-implantitis (<2.5 mm of bone loss and pockets >4 mm showing bleeding and/or pus on probing) with titanium curettes or with an ultrasonic device provides very limited clinical improvement\(^{38}\). Likewise, the evidence for the use of local or systemically delivered antibiotics in destructive peri-implant infections is incomplete and lacks a scientific basis. In practice, selection of antibiotics and regimes for systemic administration are often the same as they are used to treat aggres-sive periodontitis.

There is a need for randomised clinical trials to show the effects of systemically administered antibi-otics in the treatment of peri-implantitis. Double-blind, placebo-controlled studies are necessary in which the sole effect of antibiotics is tested. The inclusion criteria should be well defined, the smok-ing habit of the patients should be documented, the periodontal status and periodontal treatment his-tory should be described in dentate subjects, and the microbiological composition of the peri-mucosal plaque should be analysed as it was in some stud-ies\(^{32,33}\). This may be critically important since peri-
implant diseases may not always be the result of infection, as is often assumed\textsuperscript{39}.

Although locally delivered antibiotics have been shown to be effective in improving clinical parameters in peri-implantitis lesions to some extent, understanding why failures occur (implant loss, ongoing active disease) remains a key issue\textsuperscript{35,36}. A critical question for local and systemic antimicrobial treatment is which patient will benefit from which antimicrobial treatment. Sequencing of antibiotics in peri-implantitis treatment is also a critical issue and could depend on the periodontal status and the clinical parameters of the peri-implant lesion(s).

It is not known whether or not the composition of the submucosal microbiota is a determining factor for the effectiveness of an antibiotic therapy in peri-implantitis. Based on the literature on the composition of the microflora of peri-implantitis lesions, it seems that peri-implant lesions in fully edentulous patients are less complex and contains fewer periodontal pathogens in comparison to lesions in partially edentulous patients\textsuperscript{11}. Using a PCR analysis technique, Karbach et al\textsuperscript{15} found that the percentage of implants with periodontal pathogens was significantly lower in fully edentulous patients than in partially edentulous patients. This is consistent with the finding of Kocar et al\textsuperscript{16} who found that the presence of four periodontal pathogenic bacteria (\textit{A. actinomycetemcomitans}, \textit{P. gingivalis}, \textit{T. forsythia}, \textit{T. denticola}) is common in healthy peri-implant sulci of partially edentulous patients, whereas these bacterial species are virtually absent from the peri-implant sulci of completely edentulous patients. These observations may indicate that different antimicrobial strategies are possible in the control of peri-implant infections.

Peri-implantitis is a difficult disorder to treat, is time consuming and may involve invasive treatment. Prevention of these conditions rather than treating them will save a significant amount of time, money and effort. There is much to gain when proper periodontal infection control in dentate individuals is part of the pre-treatment protocol when the use of oral implants is considered. This is evident when one considers the observation that a history of periodontitis represents a risk factor for peri-implantitis\textsuperscript{40,42}. These individuals have the genetic susceptibility factor, have a certain lifestyle (smoking, stress) and they have an oral microflora that allows periodontitis to develop. Therefore it may not be surprising that these subjects also run a risk of developing peri-implantitis. The controllable factor through periodontal treatment is the oral microflora. Pre-implant measures should involve all interventions necessary to eliminate all reservoirs of anaerobes such as pockets >4 mm. Furthermore, a low bleeding index and a high standard of oral hygiene may reduce the risk of infectious peri-implant complications. Also, microbiological testing to check for the presence of residual periodontal pathogens could be part of the pre-implant treatment screening.

\section*{References}


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