Antimicrobial Treatment of Peri-implant Diseases

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Purpose: *To review the literature on the treatment of peri-implant diseases. Specific emphasis was placed on the use of antimicrobial therapy, defined as local or systemic administration of antiseptic and/or antibiotic agents.* ***Materials and Methods:*** *A search of MEDLINE, the Cochrane Controlled Trials Register, and The Cochrane Health Group Specialized Register was conducted, and articles published in English until July 31, 2003, were included. The results of experimental animal studies and human research are presented.* ***Results:*** *A variety of antimicrobial treatment regimens in combination with nonsurgical or surgical debridement with and without regenerative therapy were reported. Use of antimicrobials varied between studies with respect to type of drug, dosage, delivery system, duration, and commencement of antibiotic administration. Patient compliance and adverse effects related to the antimicrobials were mostly not mentioned.* ***Discussion:*** *While the majority of the case reports and studies presented showed positive outcomes following antimicrobial treatment, there were no non-medicated controls included, so the relative effect of the antimicrobial agent(s) cannot be evaluated.* ***Conclusions:*** *Although antimicrobials are widely used for the treatment of peri-implant diseases, evidence of their benefit is limited, and randomized, controlled human trials should be initiated where ethically possible. In addition, prospective cohort studies designed to monitor consecutive cases treated using specific treatment protocols are required.* INT J ORAL MAXILLOFAC IMPLANTS 2004; 19(SUPPL):128–139

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Biologic complications in implant dentistry include peri-implant mucositis and peri-implantitis. At the first European Workshop on Periodontology, *peri-implantitis* was defined as an inflammatory process affecting the tissues around an osseointegrated implant in function, resulting in loss of supporting bone. *Peri-implant mucositis* was defined as reversible inflammatory changes of the peri-implant soft tissues without any bone loss.[1]

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INCIDENCE OF PERI-IMPLANT DISEASES

There is limited information in the literature regarding the incidence of peri-implant diseases, as data referring to the presence or absence of peri-implantitis are often not reported. Furthermore, because of inconsistencies in peri-implant assessment procedures and definitions of peri-implant mucositis and peri-implantitis, the interpretation of data is difficult. In a systematic review of implant complications from prospective longitudinal follow-up studies of at least 5 years, the incidence of peri-implantitis in the included articles ranged from 0% to 14.4%.[2] There is recent evidence that the incidence of peri-implantitis may be higher in patients with implants replacing teeth lost because of chronic periodontitis.[3] The incidence of peri-implantitis may well be related to the number of years the implant has been in the oral cavity, and thus continuous monitoring of peri-implant conditions, provision of a supportive care program, and the implementation of well-tested protocols for the treatment of peri-implant diseases remain important.

ETIOLOGY OF PERI-IMPLANT DISEASES

Evidence for the microbial etiology of peri-implant diseases is overwhelming. Bacterial colonization of the implant surface leads to mucositis[4–6] and, if the peri-implant bone levels are affected, to peri-implantitis.[7–10] The microflora associated with peri-implantitis is complex and closely resembles that found in chronic periodontitis, with high levels and proportions of suspected periodontal pathogens including *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tanerella forsythensis*, and *Treponema denticola*.[11–19]

It is therefore not surprising that therapies proposed for the management of peri-implant diseases appear to be based on the evidence available for treatment of periodontitis. Most publications in humans report individual cases treated with combined procedures, aimed at reducing the bacterial load within the peri-implant pocket, decontaminating the implant surface, and in many cases attempting to regenerate bone. Proposed therapies include nonsurgical debridement, antimicrobial therapy, access flap surgery, implant surface decontamination, bone grafts or bone substitute grafts, barrier membranes, combinations of grafts and barrier membranes, and supportive therapy.

Treatment outcomes are most commonly assessed using criteria that include peri-implant probing depth (PD), presence of bleeding on probing (BOP), presence of suppuration, and changes in radiographic bone level or density. In animal studies, evaluation at a histologic level enables assessment of the resolution of the inflammation, and in addition, possible re-osseointegration following regenerative procedures.

The objective of this article was to review antimicrobial therapy, including the use of antiseptic and/or antibiotic agents, administered locally or systemically for the treatment of peri-implant diseases.

MATERIALS AND METHODS

Search Strategy

A search of MEDLINE, the Cochrane Controlled Trials Register, and The Cochrane Health Group Specialized Register was conducted, and articles published in English until July 31, 2003, were included. The following search terms were used: "peri-implantitis," "periimplantitis," "peri-implant mucositis," "periimplant mucositis," "treatment peri-implant infections," "treatment periimplant infections," "treatment peri-implant mucositis," "treatment periimplant mucositis," "treatment peri-implantitis," "treatment periimplantitis." Manual searches included bibliographies of previous reviews and the following journals up to July 2003: *Journal of Periodontology*, *Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, and *The International Journal of Oral & Maxillofacial Implants*.

Selection Criteria

1. All levels available in the hierarchy of evidence were included: systematic reviews, randomized controlled clinical trials, controlled clinical trials, prospective cohort studies, case reports in humans, and experimental animal studies.
2. For the treatment of peri-implant mucositis, only publications with a minimum observation period of 6 weeks following treatment, and where implants were clearly defined as having peri-implant mucositis, were included.
3. For the treatment of peri-implantitis in humans, only publications reporting a series of cases with a minimum follow-up period of 6 months, and providing data on treatment outcomes assessed by clinical probing and/or radiographic or re-entry measurements, were included.
4. For the treatment of ligature-induced peri-implantitis, only publications reporting an observation period of at least 4 months were included.

RESULTS

Antimicrobial Treatment of Peri-implant Mucositis: Human Studies

Table 1 summarizes the available evidence evaluating antimicrobial treatment of peri-implant mucositis. Three studies investigated the use of antiseptic cleansing protocols using chlorhexidine[20,21] or Listerine (Pfizer, Morris Plains, NJ).[22] One study evaluated the submucosal placement of tetracycline fibers[23] and another the submucosal application of phosphoric acid gel.[24]

These studies, which were all of short duration and involved only a small number of subjects, demonstrated that effective plaque removal from the implant crown and abutment surface resulted in resolution of inflammation in the peri-implant mucosa, probing depth reduction, and reduction of bleeding on probing.[25–27] However, there was no obvious superiority of one treatment over another in achieving these positive outcomes.

Table 1 Antimicrobial Treatment of Peri-implant Mucositis (Human Studies)

Study	Study design	Patients/ implants	Treatment procedures	Evaluation period (mo)	Treatment outcomes	Comments
Felo et al 1997[20]	Randomized comparative study, Parallel-group design	24 patients	Self- administered CHX (0.06%) irrigation (100 mL 1×/d); versus full-mouth CHX (0.12%) rinsing (2 mL)	3	PI: 1.4; marginal bleeding: 0.3; versus PI: 1.6; marginal bleeding: 0.4	Antiseptic irrigation achieved signif. lower plaque + marginal BI scores.
Porras et al 2002[21]	Controlled study, Parallel-group design	16 nonsmoking patients; 24 Ti implants, 4 HA implants	Mechanical cleansing + OHI + CHX (0.12%) irrigation + topical CHX gel (0.12%) + CHX rinsing (0.12%) 2×/d, for 10 d; versus mechanical cleansing + OHI	3	PD: 3.3 to 2.7 mm; versus PD: 3.5 to 2.6 mm	No signif. difference in reduction in mPI, mBI, BOP, or in detection of 8 suspected periodontal pathogens. More PD reduction in control group.
Ciancio et al 1995[22]	Randomized, double-blind, parallel-group design	20 patients with ≥ 2 Ti root-form implants	Antiseptic mouthrinse (Listerine) (20 mL 2×/d for 30 s); versus placebo mouthrinse (5% hydroalcohol) 2×/d for 30 s	3	PI: 2.0 to 0.8, BI: 0.6 to 0.3, and PD: 2.12 mm; versus PI: 1.8 to 1.6, BI: 0.6 to 0.5, and PD: 1.97 mm	Less plaque and bleeding in antiseptic group; however, higher PD scores. No adverse events reported. Compliance 89% in both groups.
Schenk et al 1997[23]	Controlled study, split-mouth design	8 patients, 24 Ti zircon oxide implants	Mechanical debridement (steel curettes + rubber cup polishing) + local tetracycline HCl fibers + CHX (0.2%) rinsing 2×/d for 10 d; versus mechanical debridement + CHX (0.2%) rinsing 2×/d for 10 d	3	mPI: 0.9 to 1.0 and BOP: 67% to 50%; versus mPI: 0.9 to 0.9 and BOP: 51% to 66%	In both groups, plaque scores were high at 12 weeks. Similar outcome for 2 treatment groups.
Strooker et al 1998[24]	Randomized split-mouth design	16 patients, 64 implants	Monthly phosphoric acid gel 35% (pH 1) for 1 min; versus monthly mechanical debridement (carbon fiber curettes + rubber cup)	5	GI: 0.9 to 0.3, BOP: 31% to 10%, and PD: 3.0 to 2.3 mm; versus GI: 0.8 to 0.6, BOP: 29% to 14%, and PD: 2.8 to 2.5 mm	No signif. difference between treatments in reduction of BOP or PD. No difference in frequency of detection of bacteria. Nine of 16 patients complained of pain after gel.

BI = Ainamo and Bay Bleeding Index[25]; BOP = bleeding on probing; CHX = chlorhexidine digluconate; GI = Gingival Index[26]; HA = hydroxyapatite; mBI = modified Bleeding Index[11]; mPI = modified Plaque Index[11]; OHI = oral hygiene instruction; PD = peri-implant probing depth; PI = Turesky modification of the Quigley-Hein Plaque Index[27]; Ti = titanium.

Antimicrobial Treatment of Peri-implantitis: Human Studies

Nonsurgical Debridement Combined with Antimicrobial Therapy. Table 2 describes human studies in which treatment of peri-implantitis involved nonsurgical debridement combined with antimicrobial therapy. Two prospective cohort studies evaluated the treatment of peri-implantitis using mechanical and antiseptic cleansing followed by antibiotics. In one study, systemic ornidazole (1,000 mg ×1) was administered over 10 days,[28] and in a subsequent study, tetracycline fibers were placed around the implants for 10 days.[29] Two of 30 patients in the study using tetracycline fibers required additional treatment because of persistent peri-implantitis. One of 9 patients in the study using ornidazole showed no improvement. In the remaining patients, probing depth reduction and resolution of inflammation were achieved and maintained over a 1-year observation period. Microbiologic monitoring was performed in both studies, and a significant reduction in the proportion of gram-negative anaerobes[28] and in the frequency of detection of several suspected periodontal pathogens was observed.[29]

In another study, a similar protocol including mechanical debridement, chlorhexidine irrigation, and systemic antibiotics, which were selected on the basis of antimicrobial susceptibility testing, resulted in resolution of inflammation, as demonstrated by reductions in peri-implant probing depth ranging from 1.3 to 1.5 mm at 6 months.[30] Patients in this comparative study had initial bone loss greater than 50% of the implant length and following nonsurgical antimicrobial therapy entered a surgical phase aimed at eliminating the peri-implant defect by bone regeneration. In all 3 studies, nonsurgical antimicrobial therapy resulted in only limited radiographic bone fill. The relative importance of mechanical debridement, topical antimicrobials, and systemic or local antibiotics cannot be determined from these studies.

Antimicrobial Therapy Combined with Surgical Debridement. There are no human studies comparing the effect of surgical debridement with or without systemic or local antibiotics.

Antimicrobial Therapy Combined with Regenerative Surgery. Table 3 includes reports that combined regenerative surgical procedures with systemic antibiotics.

Behneke and coworkers[31] presented results of treatment of 25 implants in 17 patients with initial mechanical and antiseptic therapy for 1 month, followed by surgical access, implant surface decontamination, and autogenous bone grafting. Systemic antibiotics were prescribed postoperatively for 7 days. Considerable probing depth reduction and radiographic bone gain was reported at 1 and 3 years of follow-up; however, at 3 years only 10 of the original 25 implants were evaluated. Complications included infection and graft removal for 2 implants and flap dehiscence for another 4 implants.

Treatment of peri-implantitis using barrier membranes combined with antimicrobial therapy was described in 2 case series involving 9 patients.[32,33] Following a short period of antiseptic therapy, both authors used a nonresorbable e-PTFE membrane followed by postoperative systemic antibiotics and achieved resolution of inflammation, probing depth reduction, and radiographic bone gain. Membrane exposure was reported in more than half of the cases.

Table 3 also includes 2 publications reporting the treatment of peri-implantitis using antimicrobial therapy combined with barrier membranes and graft materials. Khoury and Buchmann,[30] in a comparative study, initiated systemic antibiotics at 4 weeks preoperatively for 1 week and administered them again for 7 days postoperatively. The antibiotic was chosen based on antimicrobial susceptibility test results. Haas and associates[34] investigated regenerative surgery without prior initial therapy, prescribing penicillin (Augmentin, SmithKline Beecham, Mayenne, France) for 5 days postoperatively. Various methods for implant surface decontamination were used, including photosensitizing treatment[34] and chlorhexidine + citric acid + hydrogen peroxide + saline irrigation.[30] Both studies reported radiographic bone fill and an improvement of the soft tissue conditions in the majority of cases. Two implant losses were reported in the series by Haas and associates,[34] and early membrane exposure was a common complication in both studies.

Antimicrobial Treatment of Ligature-Induced Peri-implantitis: Animal Studies

Animal studies investigating antimicrobial treatment of experimental ligature-induced peri-implantitis are described in Table 4.

In a study by Ericsson and colleagues, the effect of antibiotic therapy with or without debridement of the surgical defect was evaluated.[35] Systemic antibiotic therapy (amoxicillin 375 mg ×2 + metronidazole 250 mg ×3), administered for 3 weeks, starting 1 week prior to flap surgery, was found to successfully reduce the inflammatory lesion when combined with local debridement and decontamination of the implant surface. There was no new bone formation. The control implants, where no local treatment was provided, had persistent infection. These results emphasize the importance of local mechanical debridement to disrupt the biofilm when systemic antibiotics are administered.

Table 2 Treatment of Peri-implantitis with Nonsurgical Antimicrobial Therapy (Human Studies)

Study	Study design	Patients/ implants	Treatment procedures	Antimicrobial	Adverse effects	Evaluation period (mo)	Comments
Mombelli/Lang 1992[28]	ProsC	9 patients, 9 implants; ITI F type/Bonefit	OHI + mechanical cleaning + CHX (0.5%) irrigation + systemic antibiotic for 10 d + daily irrigation CHX (0.2%) for 10 d + supportive therapy	ORN (1,000 mg ×1)	No improvement in PD in 1 patient (1 implant)	12	Sig reductions in BI (1.6 to 0.7), PD (5.9 to 3.4 mm), and proportion gram-negative anaerobes (41% to 19%)
Mombelli et al 2001[29]	ProsC	25 patients, 30 implants; ITI hollow screws/ cylinders, 3 full-body screws	OHI + mechanical cleaning + tetracycline fibers for 10 d; + CHX (0.2%) mouthrinse for 2 wk + supportive therapy	TET HCl fibers	Persistent peri-implantitis in 2 patients (2 implants)	12	Sig reductions in mBI (0.95 to 0.37), PD (4.7 to 3.5 mm), 6% radiographic bone fill, CAL change (2 mm in deepest pockets); decrease in detection of some suspected periodontal pathogens
Khoury/Buchmann 2001[30]	CS, initial therapy prior to surgical therapy	25 patients, 41 implants with bone loss > 50% implant length; IMZ/Friadent	CHX irrigation (0.2%) + mechanical cleaning + susceptibility test + systemic antibiotics for 1 wk + weekly prophylaxis + OHI	AMX, MET, TET, CLIN, CIPRO	Not reported	6	PD reduction: range 1.3 to 1.5 mm; radiographic bone fill: range 0.2 to 0.3 mm

AMX = amoxicillin; BI = Ainamo and Bay Bleeding Index[25]; CAL = clinical attachment level; CHX = chlorhexidine digluconate; CIPRO = ciprofloxacin; CLIN = clindamycin; CS = case series; mBI = modified Bleeding Index[11]; MET = metronidazole; OHI = oral hygiene instruction; ORN = ornidazole; PD = peri-implant probing depth; ProsC = prospective cohort study; TET = tetracycline.

Table 3 Treatment of Peri-implantitis with Regenerative Surgery and Systemic Antibiotics (Human Studies)

Study	Study design	Patients/ implants	Systemic antibiotic	Treatment procedures	Evaluation period	Treatment outcome	Adverse events
Khoury/ Buchmann 2001[30]	Comp	1. 7 patients/12 implants; 2. 11 patients/20 implants; 3. 7 patients/9 implants; IMZ/Friadent	AMX, MET, TET, CLIN, ERY, CIPRO after susceptibility testing for 2 wk (1 wk at 4 wk preop + 1 wk at 1 wk postop)	Initial therapy + surgical debridement + CHX irrigation + citric acid (pH1) for 1 minute + H_2O_2 + saline (0.9%) + 1. AB, 2. AB + e-PTFE, 3. AB + collagen membrane. Submerged healing, supportive care for 3 to 6 mo	3 y	1. PD: 6.5 to 2.9 mm, PBL: 6.9 to 4.1 mm. 2. PD: 6.7 to 2.8 mm, PBL: 7.4 to 4.3 mm. 3. PD: 6.4 to 5.1 mm, PBL: 7.0 to 5.1 mm. Radiographic bone fill: 1. 2.2 mm, 2. 2.5 mm, 3. 1.7 mm	59% of barrier- treated implants were compromised by early posttherapy complications (membrane exposures, dehiscence, fistula, sequestrum)
Behneke et al 2000[31]	CR	17 patients, 25 implants; ITI (TPS surface)	MET (400 mg ×2) for 7 d postop	Initial therapy: mechanical debridement + irrigation iodine (1×/wk for 1 mo); access flap + air-powder abrasive + saline + AB augmentation. Supportive care for 3 mo; nonsubmerged healing	6 mo to 3 y	1 y (18 implants): PD: 5.3 to 2.2 mm. At 3 y (10 implants): PD: 5.3 to 1.6 mm and complete refill of angular bone defects	Flap dehiscence (4 lesions), graft failure (2 lesions)
Jovanovic et al 1992[32]	CR	7 patients, 10 implants; IMZ/Brånemark/TPS	TET (250 mg × 4) for 7 d postop	Surgical debridement + air powder+ chloramine-T + saline + e-PTFE; nonsubmerged healing	6 mo	PI: 1.7 to 0.6; GI: 2.1 to 0.3; PD: 6.8 to 4.1 mm	Membrane exposure (× 3)
Hämmerle et al 1995[33]	CR	2 patients, 2 implants; ITI (hollow screw, TPS surface)	MET (250 mg ×3) and AMX (375 mg × 3) for 10 d postop	CHX (0.2%) irrigation, 5 d later surgical debridement + CHX (0.2%) and saline irrigation + e-PTFE; nonsubmerged healing. Healing period: CHX (0.2%) gel 2×/d until membrane removal + supportive therapy	12 mo after membrane removal	PD: 6.7 to 3.5 mm; PAL gain: 1.8 mm; mean radiographic bone gain: 2.2 mm	Membrane exposures and removal after 4 and 6 mo, respectively
Haas et al 2000[34]	CR	17 patients, 24 implants; IMZ	AUG for 5 d postop	Surgical debridement + toluidine blue (100 µg/mL) + saline rinsing + soft laser light (906 nm) + AB + e-PTFE. Submerged healing, supportive care	Mean 9.5 mo	No clinical parameters assessed. Radiographic mean bone fill: 2.0 mm (range –0.5 to 7.3 mm); 36% defect fill (range –14% to 100%)	All membranes exposed at 3 weeks; 2 implants failed

AB = autogenous bone; AMX = amoxicillin; AUG = augmentin; CHX = chlorhexidine digluconate; CIPRO = ciprofloxacin; CLIN = clindamycin; Comp = comparative study; CR = case reports; e-PTFE = expanded polytetrafluoroethylene membrane; ERY = erythromycin; GI = Gingival Index[26]; MET = metronidazole; PAL = probing attachment level; PBL = probing bone level; PD = peri-implant probing depth; PI = Turesky modification of the Quigley-Hein Plaque Index[27]; surgical debridement/curettage = removal of granulation tissue; TET = tetracycline; TPS = titanium plasma sprayed.

The importance of implant surface characteristics[36] and implant surface decontamination[9,37,38] for peri-implantitis treatment outcome has been addressed in animal studies incorporating systemic antimicrobials within the treatment protocol.

In the majority of studies in Table 4, postoperative systemic antibiotics were used in combination with local debridement and regenerative procedures. Barrier membranes were evaluated in 2 studies.[39,40] Other treatment protocols applied bone augmentation procedures using membranes combined with bone grafts (including demineralized freeze-dried bone allograft,[41,42] anorganic bovine bone,[43–45] and autogenous bone[10,46]) or bone substitutes (hydroxyapatite[41,42]). Hanisch and coworkers[47] evaluated the use of recombinant human bone morphogenetic protein-2 and systemic antibiotics for treatment of peri-implantitis.

Antimicrobial therapy using lethal photosensitization in conjunction with surgical debridement was investigated by Shibli and associates[48] for the treatment of ligature-induced peri-implantitis.

All experimental treatments listed in Table 4 resulted in resolution of the inflammatory lesion and new bone formation, while some protocols demonstrated varying degrees of re-osseointegration. The most common choice of systemic antibiotic was a combination of metronidazole and amoxicillin, or metronidazole alone. The various outcomes of the above-mentioned surgical protocols in combination with the administration of antimicrobials are reviewed elsewhere.[49]

Conclusions from the Available Evidence

Antimicrobial Treatment of Peri-implant Mucositis. From the available evidence it may be concluded that the treatment of peri-implant mucositis should include patient motivation and instruction in oral hygiene procedures, followed by mechanical/chemical plaque removal using a combination of professional and self-performed care.

Antimicrobial Treatment of Peri-implantitis with Nonsurgical or Surgical Therapy: Human Studies. While the results of the majority of human case reports and studies presented suggest positive clinical and radiographic treatment outcomes, some cases treated were unsuccessful or required additional therapy.

The antibiotic regimens used varied between studies with respect to type of antibiotic, dosage, delivery system, duration, and commencement of antibiotic therapy. Adverse effects related to the antimicrobial agents and patient compliance were not considered. Antimicrobial susceptibility testing was done prior to selection of the antibiotic in only 1 study.[30] There were no controls included, and the relative importance of mechanical debridement, topical antimicrobials, and systemic or local antibiotics cannot be determined from these studies. There is insufficient evidence to recommend a particular anti-infective protocol for the treatment of peri-implantitis.

Antimicrobial Treatment of Ligature-Induced Peri-implantitis: Animal Studies. All experimental studies resulted in resolution of the inflammatory lesion and new bone formation, while some protocols demonstrated varying degrees of re-osseointegration. The most common choice of systemic antibiotic was metronidazole and amoxicillin combined, or metronidazole alone. However, there are no animal studies comparing local therapy with or without systemic antibiotics, and hence the value of adjunctive antimicrobial therapy cannot be evaluated.

DISCUSSION AND CLINICAL IMPLICATIONS

Following successful periodontal and implant therapy, patients should be offered an individualized supportive care program. Diagnosis of peri-implant disease requires continuous systematic monitoring of the peri-implant tissue conditions. Parameters recommended to assess the absence, presence, and severity of disease include: presence of plaque or calculus, peri-implant probing depth in relation to baseline measurements obtained at the time of prosthetic reconstruction, presence of bleeding on gentle probing, presence of suppuration, and, if indicated, radiographic evaluation.

Probing depths for conventionally placed 1-stage implants generally range between 2 and 4 mm under healthy conditions.[50] In sites of esthetic priority, where the implant shoulder has intentionally been placed submucosally, or where mucosal tissues are thick, deeper baseline probing depths may be present. Increases in probing depths above these baseline values should be viewed as a sign of peri-implant disease.

A systematic approach for the prevention and treatment of peri-implant disease was suggested by Lang and coworkers.[51] This protocol, referred to as *cumulative interceptive supportive therapy* (CIST), includes 4 treatment modalities (*A*, mechanical debridement; *B*, antiseptic treatment; *C*, antibiotic treatment; and *D*, regenerative or access/resective surgery), which should be used in sequence in a cumulative fashion, depending on the diagnosis made at each recall.

Although this protocol has not been assessed in its entirety, 2 prospective cohort studies have been

Table 4 Treatment of Ligature-induced Peri-implantitis (Animal Studies)

Study	Animals/implants	Systemic antibiotic	Treatment procedures	Implant surface decontamination	Healing period	Treatment outcomes
Ericsson et al 1996[35]	5 dogs, 10 implants (Brånemark machined surface)	AMX (375 mg ×2) and MET (250 mg ×3) for 3 wk starting 1 wk prior to surgery	1. Access flap; 2. untreated control	Delmopinol 1%; abutments autoclaved	4 mo	1. Resolution of inflammation, no bone formation; 2. Persistent infection
Persson et al 2001a[36]	4 dogs, 8 implants; ITI 1. 4 machined surface, 2. 4 SLA surface	AMX (250 mg ×2) and MET (250 mg ×2) for 17 d starting 3 d prior to surgery	Access flap	Cotton pellet soaked in saline	6 mo	Bone regeneration (% of original defect surface area): 1. 72%, 2. 77%; Re-osseointegration: 1. 22%, 2. 84%; Radiographic bone gain: 1. 0.8 mm, 2. 1.4 mm; "spontaneous exposure" of some implants after 1 month
Persson et al 1999[37]	4 dogs, 24 implants (Brånemark machined surface)	AMX (500 mg/d) and MET (750 mg/d) starting 2 d before surgery for 3 wk	Access flap	1. Rotating brush + pumice; 2. cotton pellet soaked in saline	7 mo	Bone regeneration (% of original defect surface area): 1. 59%, 2. 64%; soft tissue capsule between bone and implant
Persson et al 2001b[38]	2 dogs, 16 implants (12 test/4 control) (Brånemark machined surface)	AMX (500 mg × 1) and MET (250 mg × 1) for 3 wk starting 1 wk prior to surgery	1. Access flap + replacement of coronal implant part; 2. access flap	Cotton pellet soaked in saline	4 mo	1. Osseointegration identified on the replaced implant part = 35% osseointegration; 2. defects "filled with new bone separated from the fixture surface by dense connective tissue"
Persson et al 1996[39]	5 dogs, 30 implants (Brånemark machined surface)	AMX (375 mg × 2) and MET (250 mg × 3) for 3 wk postop	1. Access flap + 1% e-PTFE; 2. untreated control	Delmopinol	4 mo	1. Elimination of inflammatory infiltrate and "formation of a dense CT capsule"; 2. persistent infection and "no resolution of peri-implant lesion"
Wetzel et al 1999[40]	7 dogs, 39 implants (ITI TPS surface, SLA surface, machined surface)	MET (20 mg/kg) for 10 d starting 2 wk prior to surgery	1. Access flap; 2. access flap + e-PTFE	CHX irrigation	6 mo	Bone regeneration (% of original defect surface area): 1. 14% to 31%, 2. 62% to 83%; membrane exposures
Hürzeler et al 1995[41]	4 dogs, 24 implants (Brånemark machined surface)	MET (250 mg × 1) for 3 wk starting 2 wk prior to surgery	1. Access flap; 2. access flap + HA; 3. access flap + DFDBA; 4. access flap + e-PTFE; 5. access flap + HA + e-PTFE; 6. access flap + DFDBA + e-PTFE	Air-powder abrasive for 30 s	4 mo	New bone at clinical re-entry: 1. 0.5 mm; 2. 1.8 mm; 3. 2.2 mm; 4. 3.6 mm; 5. 3.2 mm; 6. 3.8 mm
Hürzeler et al 1997[42]	7 dogs, 42 implants (Brånemark machined surface)	MET (250 mg × 1) for 3 wk starting 2 wk prior to surgery	1. Access flap; 2. access flap + HA; 3. access flap + DFDBA; 4. access flap + e-PTFE; 5. access flap + HA + e-PTFE; 6. access flap + DFDBA + e-PTFE	Air-powder abrasive for 30 s	5 mo	Bone regeneration: 1. 0.5 mm; 2. 1.3 mm; 3. 1.6 mm; 4. 2.5 mm; 5. 2.4 mm; 6. 3.0 mm. Re-osseointegration: 1. 0.3 mm; 2. 0.9 mm; 3. 0.9 mm; 4. 1.0 mm; 5. 2.3 mm; 6. 2.2 mm
Machado et al 1999[43]	4 animals, 16 implants (Napio System Ti implants)	MET (250 mg × 1) for 3 wk starting 2 wk prior to surgery	1. Access flap; 2. access flap + e-PTFE; 3. access flap + bovine anorganic bone; 4. access flap + bovine anorganic bone+ e-PTFE	Air-powder abrasive for 30 s	5 mo	Bone regeneration at clinical re-entry: 1. 0.9 mm; 2. 1.4 mm; 3. 1.6 mm; 4. 1.6 mm. One membrane exposure at 1 wk

Table 4 Treatment of Ligature-induced Peri-implantitis (Animal Studies) continued

Study	Animals/implants	Systemic antibiotic	Treatment procedures	Implant surface decontamination	Healing period	Treatment outcomes
Machado et al 2000[44]	5 dogs, 20 implants (Napio System)	MET (250 mg × 1) for 3 wk starting 2 wk prior to surgery	1. Access flap; 2. access flap + e-PTFE; 3. access flap + bovine anorganic bone; 4. access flap + bovine anorganic bone + e-PTFE	Air-powder abrasive for 30 s	5 mo	Re-osseointegration (reference: 6 most coronal threads): 1. 27%; 2. 31%; 3. 28%; 4. 27%
Nociti et al 2001[45]	5 dogs, 30 implants (Napio System)	MET (250 mg/day) for 3 wk starting 2 wk prior to surgery	1. Access flap; 2. access flap + bovine anorganic bone; 3. access flap + e-PTFE; 4. access flap + collagen membrane; 5. access flap + e-PTFE + bovine anorganic bone; 6. access flap + collagen membrane + bovine anorganic bone	Air-powder abrasive for 30 s	4 mo	Bone regeneration (reference: previous vertical defect height): 1. 14%; 2. 21%; 3. 19%; 4. 22%; 5. 20%; 6. 28%. Four membrane exposures
Hanisch et al 1997[47]	4 monkeys, 31 implants (HA coated)	CEPH (50 mg/kg × 3) for 1 wk	1. Access flap + rh BMP-2; 2. access flap + vehicle control	Citric acid + air-powder abrasive	4 mo	Bone regeneration/re-osseointegration: 1. 2.6 mm (40% re-osseointegration); 2. 0.8 mm (9% re-osseointegration). Implant exposure through oral mucosa
Schou et al 2003a[9]	8 monkeys, 57 implants (TPS surface)	AMP (17 mg/kg × 3) and MET (13 mg/kg × 3) 12 d starting 2 d before surgery	Access flap + AB+ e-PTFE	1. Air-powder abrasive unit (5 min) + citric acid (2 min); 2. air-powder abrasive unit (5 min); 3. gauze soaked in saline (5 min) + citric acid (2 min); 4. gauze soaked alternately in CHX + saline (5 min)	6 mo	Total bone regeneration: 39% to 46% re-osseointegration (reference previous defect); no difference between methods; 36% membrane exposure
Schou et al 2003b,c[10,46]	8 monkeys, 61 implants (ITI TPS surface)	MET (13 mg/kg × 3) and AMP (17 mg/kg × 3) for 12 d starting 2 d before surgery	1. Access flap + AB + e-PTFE; 2. access flap + AB; 3. access flap + e-PTFE; 4. access flap	Gauze soaked alternately in CHX and saline (5 min)	6 mo	Healthy peri-implant tissues. Radiographic bone fill: 1. 4.7 mm; 2. 4.0 mm; 3. 3.0 mm; 4. 1.9 mm. Re-osseointegration (reference original defect): 1. 45%; 2. 22%; 3. 21%; 4. 14%; 38% membrane exposure
Shibli et al 2003[48]	6 dogs, 19 implants (1. cpTi, 2. TPS, 3. HA, 4. AE)	None	Access flap + e-PTFE	Lethal photosensitization w/toluidine blue+ diode laser	5 mo	Bone regeneration (% of original defect): 1. 27%; 2. 40%; 3. 48%; 4. 27%. Re-osseointegration: 1. 25%; 2. 25%; 3. 16%; 4. 17%

AB = autogenous bone; AE = acid etched; AMP = ampicillin; AMX = amoxicillin; CEPH = cephazolin; CHX = chlorhexidine digluconate; cpTi = commercially pure titanium; CT = computerized tomography; DFDBA = demineralized freeze-dried bone allograft; e-PTFE = expanded tetrafluoroethylene membrane; HA = hydroxyapatite; MET = metronidazole; rhBMP-2 = recombinant human bone morphogenetic protein-2; SLA = sandblasted, large-grit, and acid-etched (Straumann); TPS = titanium plasma spray.

published evaluating the treatment modalities A + B + C.[28,29] Furthermore, an ongoing prospective cohort study reported significant improvements in clinical and microbiologic parameters at 3 months in the treatment of peri-implantitis using local application of minocycline microspheres as part of the CIST protocol.[52] In addition, Khoury and Buchmann[30] reported on the administration of systemic antibiotics as part of an initial phase of therapy prior to surgery.

Limitations to nonsurgical therapy may necessitate surgical intervention. According to the CIST protocol, peri-implantitis lesions with more than 2 mm of bone loss require initial therapy followed by either access/resective or regenerative surgery. A number of issues associated with surgical treatment of peri-implantitis have been investigated, including methods for implant surface decontamination. Several protocols have been suggested, including air-powder abrasives, citric acid, or antimicrobial agents. In a recent animal study, Schou and colleagues[9] compared 4 decontamination protocols and concluded that alternating between gauze soaked in chlorhexidine and gauze soaked in saline for cleaning was the preferred method. There is no evidence for the necessity of smoothing mechanical implant surfaces.

It is apparent that pre- and postoperative systemic antibiotics are frequently empirically prescribed in conjunction with regenerative surgical procedures. Evidence for an advantage in using adjunctive systemic antibiotics is lacking. However, the severity and aggressive nature of the inflammatory lesion around implants with peri-implantitis recently documented by Gualini and Berglundh[53] suggests that the use of systemic antimicrobials in combination with surgical therapy may be indicated.

While there is insufficient evidence to recommend a specific postoperative antibiotic regimen, the most commonly used antibiotics among published protocols (Tables 3 and 4) are metronidazole and amoxicillin. Systemic metronidazole alone or in combination with amoxicillin has been shown to be effective in suppressing gram-negative anaerobic microorganisms generally associated with peri-implantitis in humans.[54] There is evidence that in some instances peri-implantitis may be associated with organisms such as *Staphylococcus spp*,[55] *Enterobacter spp*, and yeasts.[18] Based on these findings, microbial diagnosis may be advantageous prior to antibiotic selection.

It should be emphasized that a prerequisite for successful antimicrobial therapy is the establishment and maintenance of proper oral hygiene and supportive care at regular intervals. With regard to maintenance, there is no evidence that the use of powered or sonic toothbrushes is superior to manual brushing for efficacy in plaque removal around implants.[56]

CONCLUSIONS

The conclusions of this review are similar to those of a recent systematic review by Klinge and associates.[57] Evidence for antimicrobial treatment of peri-implantitis is limited, and randomized, controlled trials should be initiated where ethically possible. There is a need to determine whether antimicrobials used for periodontal therapy are effective for the treatment of peri-implant diseases. With respect to antimicrobial treatment protocols, there is limited information as to what extent initial improvement is sustained over the long term. There are no studies investigating the influence of defect characteristics or patient-related factors on treatment outcome. Additional prospective cohort studies designed to monitor consecutive cases treated using specific treatment protocols are recommended. Until the results of such trials are available, the most logical and evidence-based protocol for use in clinical practice is cumulative interceptive supportive therapy (see group 4 consensus statement).

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