Review

Systemic antibiotics and the risk of superinfection in peri-implantitis

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Abstract

Peri-implantitis has emerged in the last few years as a complication difficult to resolve. The etiopathogenesis consensus is mainly attributed to bacteria. Following the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines, a PubMed/Medline literature search was performed using the US National Library of Medicine database up to 2015 to analyze available scientific data on the rationale and risk of superinfection associated to systemic antimicrobials in human peri-implant disease. A hand search was also conducted on relevant medical and microbiology journals. The methodological index for non-randomized studies (MINORS) was independently assessed for quality on the selected papers. Proposed combined therapies use broad-spectrum antibiotics to halt the disease progression. A major associated risk, particularly when prescribed empirically without microbiological follow-up, is the undetected development of superinfections and overgrowth of opportunistic pathogens difficult to eradicate. Peri-implant superinfections with opportunistic bacteria, yeast and viruses, are plausible risks associated to the use of systemic antibiotics in immunocompetent individuals. Lack of microbiological follow-up and antibiotic susceptibility testing may lead to ongoing microbial challenges that exacerbate the disease progression. The increased proliferation of antimicrobial resistance, modern implant surface topography and indiscriminate empiric antibiotic regimens may promote the escalation of peri-implant disease in years to come. A personalized 3-month supportive therapy may help prevent risks by sustaining a normal ecological balance, decreasing specific pathogen proportions and maintaining ideal plaque control.

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1. Introduction

Osseointegrated dental implants have become a predictable treatment option in providing function in partial or total edentulism, delivering high success rate outcomes long term (Albrektsson, Zarb, Worthington, & Ericsson, 1986). However, with an estimated twelve million implants placed annually worldwide, peri-implant disease has increasingly become a complication, often difficult to resolve (Persson, Samuelsson, Lindahl, & Renvert, 2010a; Esposito, Grusovin, & Worthington, 2012; Albrektsson, Dahlen, Jemt, Sennerby, Turri, & Wennerberg, 2014).

Controversy exists regarding disease initiation, namely whether specific pathogenic microbiota are indeed the true initiators of bone loss around implants or if they are secondary to a disbalanced foreign body reaction coupled with background factors such as poorly fabricated implants placed by unqualified clinicians (Albrektsson et al., 2014; Qian, Wennerberg, & Albrektsson, 2012). Nevertheless, the European Federation of Periodontology consensus proposed that bacteria are the sole cause of peri-implant disease with associated risk factors such as poor oral hygiene, history of periodontitis, diabetes or smoking (Linde, Meyle, Group D of European Workshop on Periodontology).

Regardless of the initiating etiological factors, there is agreement that the disease process is exacerbated and maintained by specific microbial infection with bacteria and possibly viruses (Rams, Degener, & van Winkelhoff, 2014; Verdugo et al., 2015a; Verdugo, Castillo, Castillo, & Uribarri, 2015; Heitz-Mayfield, Salvi, Mombelli, Faddy, & Lang, 2012). Specific microbial contamination has been shown to impair osteogenesis, and increased bone loss has been associated with the presence of key anaerobic species and salivary Epstein-Barr virus (EBV) (Verdugo et al., 2012).

Therefore, some research groups have proposed combined, surgical and non-surgical, therapies where systemic antibiotics are administered to empirically target specific putative bacteria (Rams et al., 2014a; Heitz-Mayfield et al., 2012). The risks associated with empiric therapy are not only potential antibiotic resistance but, most importantly, the development of superinfections difficult to eradicate (Rams, Degener, & van Winkelhoff, 2014a; Rams, Degener, & van Winkelhoff, 2014b). Peri-implant opportunistic infections may be a significant risk associated with empiric broad-spectrum antibiotic regimens in immunocompetent individuals. The negative impact of antimicrobial agents on the normal protective microflora has been documented for decades (Sullivan, Edlund, & Nord, 2001). The human oropharyngeal, intestinal and vaginal ecological balance can be altered after antibiotic exposure, favoring the overgrowth of opportunistic pathogens (Sullivan et al., 2001).

Lack of follow-up and antibiotic susceptibility testing may leave specific ongoing microbial challenges difficult to eliminate, allowing disease progression to perpetuate. So far, superinfections have not been documented with the use of broad-spectrum antibiotics in peri-implant disease. However, there have been reports of rapidly progressive, non-responsive to treatment peri-implantitis, in cases where broad-spectrum antibiotic therapy was used (Emrani, Chee, & Slots, 2009; van Winkelhoff & Wolf, 2000). Indeed, the increase of subgingival superinfecting agents, such as, Enterobacter, Candida, or Staphylococcus species, can flourish after the administration of systemic antimicrobials (Helovuo, Hakkarainen, & Paunio, 1993).

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![Fig. 1. Search strategy flowchart summary of systematic review following PRISMA guidelines.](image-url)
The present study was conducted to review available scientific data on the rationale and to qualitatively assess the potential risk of superinfection after systemic antimicrobials in human peri-implant disease.

2. Methodology and quality assessment

The focused PICO question for the present review is: is there a risk of developing a superinfection in peri-implantitis lesions after the use of systemic antimicrobials?

The present systematic review work was conducted following the guidelines (www.prisma-statement.org) of the preferred reporting items for systematic reviews and meta-analysis (PRISMA). A literature search was performed on Medline using the PubMed database of the US National Library of Medicine, Scielo, Lilacs, OVID and Google Scholar up to 2015. The following key words were used: (peri-implantitis OR peri-implantitis) AND (treatment OR therapy OR therapeutics) AND (anti-bacterial agent OR antibiotics OR anti-infective agent OR antimicrobial). The search used the MeSH browser and was limited to papers published in English; humans; clinical trials; randomized clinical trials (RCT); and meta-analysis. The search was further refined by using the combination of terms: peri-implantitis AND treatment AND antibiotics AND opportunistic infections AND superinfection. Also; a hand search was performed in the following journals: Clinical Implant Dentistry and Related Research; Clinical Oral Implant Research; Clinical Oral Investigations; Journal of Clinical Periodontology; Journal of Periodontology; International Journal of Oral and Maxillofacial Implants and Medicina Oral Patología Oral Cirugía Bucal. Titles and abstracts were screened for relevance. Papers repeated or with missing data; case reports and animal studies were excluded. For the purpose of developing scientific debate and further address the issue on the concept and rational of antibiotic-associated/induced superinfections, additional scientific articles from the medical literature were selected for evaluation. The methodological index for non-randomized studies (MINORS) was independently assessed for quality on the selected papers (Table 2) by two of the authors.

The quality assurance of the present systematic study was achieved by conducting the review through independent screening by two reviewers, resolution of disagreement by consensus, discarding of papers whenever a consensus was not reached, and duplicate data extraction.

3. Results

The initial literature search generated 652 articles of which 81 were potentially relevant for analysis (Fig. 1). After screening titles and abstracts a total of 19 studies were reviewed. A final full-text evaluation selected 7 clinical studies (Tables 1 and 2) and one review (Esposito et al., 2012) for analysis based on the aforementioned inclusion criteria. Due to the scarcity of data on the particular focus question, the heterogeneity of data reported, and lack of microbiological follow-up of most reviewed studies, a statistical meta-analysis is not feasible at this point. Therefore, the present systematic review performs a qualitative evaluation of the existing published scientific data to critically appraise and analyze relevant information from selected studies to summarize the findings on a clearly focused area. Furthermore, to enhance the systematic debate on the concept and rationale of antibiotic-induced superinfections, additional scientific data from the medical literature are selected for evaluation and discussion.

The use of systemic antimicrobials has been indicated in distinct clinical scenarios of severe and aggressive forms of rapidly progressive periodontitis in patients presenting with specific microbial profiles (Herrera, Alonso, León, Roldán, & Sanz, 2008). However, there is, in fact, no established protocol for the use of antibiotic therapy in destructive periodontitis (Haffajee, Socransky, & Gunsolley, 2003). Likewise, a similar lack of protocol exists in the treatment of peri-implant disease.

3.1. Antimicrobial resistance and the risk of thriving superinfecting pathogens

The reduced vulnerability to anti-infective agents and pathogenic synergism originates from the ability to organize in microbial communities or biofilms (Marsh, 2005). If the subgingival biofilm is not sufficiently disrupted, by non-surgical or surgical means, the antimicrobial agent will not be as effective, and thus, the development of bacterial resistance will be more likely to emerge. Antibiotic resistance is due to a number of factors, such as, the biofilm extra-cellular matrix (Mah et al., 2003), the different bacterial physiological phases within the biofilm (Anderfi, Zalier, Roe, & Stewart, 2003), the potential horizontal gene transfer (Roberts, Pratten, Wilson, & Mullany, 1999), quorum sensing communication between bacterial cells (Roberts & Mullany, 2006) and their pathogenic ability to invade host cells, such as, epithelial cells and connective tissue (Eick & Pfister, 2004).

Strains of Streptococcus oralis recovered from a subgingival biofilm were shown to pass on doxycycline resistance, through horizontal gene transfer, to other species, in patients undergoing periodontal therapy with the antibiotic (Warburton, Palmer, Munson, & Wade, 2007). Similar transfer has been widely demonstrated between superinfecting bacteria, in particular, Enterococcus faecalis and Staphylococcus aureus, with different antibiotics (Weigel et al., 2003). Enterobacter species have developed a reputation for their ability to acquire and transfer multidrug resistance to a number of antibiotics such as beta-lactams, tetracyclines, aminoglycosides and even quinolones (Sanders & Sanders, 1997; Choi et al., 2008; Naesens, Ursi, Van Schaeren, & Jeuissen, 2009). Conversely, systemic doxycycline therapy in periodontitis patients has yielded a subgingival overgrowth of a 10-fold increase of superinfecting agents, such as, enteric rods, yeasts and staphylococci (Rams, Babalola, & Slots, 1990).

Certain strains of S. aureus periodontal isolates, one of the most common superinfecting bacteria, have been shown to produce a leukotoxin capable of destroying the human neutrophil first line of defense (Iwase, Slots, Berthold, & Taichman, 1990). Their potent endotoxins coupled with their ability to invade human cells and connective tissue could exacerbate oral tissue breakdown around dental implants that lack a well-vascularized periodontal ligament space (Emrani et al., 2009; van Winkelhoff & Wolf, 2000; Eick & Pfister, 2004; Sanders & Sanders, 1997; Iwase et al., 1990; Martin, Wächtler, Schaller, Wilson, & Hube, 2011).

Absent from healthy implants sites, isolates of Candida spp. and enteric rods have been reported in up to 55% of peri-implantitis lesions (Leonhardt, Renvert, & Dahlén, 1999). The pathogenic assets of Candida albicans can make this microorganism difficult to eradicate due to its capacity to invade host cells, form hyphae, secrete proteinases, and interact with communal streptococci to synergistically promote its virulence (Martin et al., 2011; Xu et al., 2014). Long term C. albicans infection may induce persistent and chronic tissue destruction through pro-inflammatory cytokine up-regulation (Martin et al., 2011; Dngari-Bagtzoglou, Kasheleva, & Villar, 2004). The degree of cytolytic activity seems to trigger interleukin-1βalpha from C. albicans-infected oral epithelial cells to increase cytokine secretion from uninfected epithelial cells (Dngari-Bagtzoglou et al., 2004).

Another superinfecting agent that can exacerbate tissue breakdown and further alter the ecological balance of peri-implant diseased tissues is Epstein-Barr virus (EBV). Recent human
research has shown that peri-implantitis lesions were 14 times more likely to be infected with the virus than healthy sites, and 3 times more likely than the patient's saliva within the same individual giving EBV a 90% positive predictive value for peri-implantitis infection (Verdugo, Castillo, Castillo, et al., 2015). Notably, research has shown that periodontitis lesions can aggravate, if infected by EBV, correlating disease severity with its presence (Vincent-Bugnas et al., 2013; Kato, Imai, Ochiai, & Ogata, 2013). EBV and Porphyromonas gingivalis have been shown to act synergistically to potentiate disease progression and tissue destruction (Kato et al., 2013). The likelihood of acquiring periodontitis was 4.7 times higher when the two pathogens were together in deep periodontal pockets of individuals with chronic periodontitis versus over two times when the pathogens were found alone (Kato et al., 2013). A different study showed that patients with clinical symptoms could be over 3 times more likely to be infected with EBV than asymptomatic ones, and saliva EBV positive individuals were 7 and 3.5 times more likely to yield granulation tissue contamination with Tannerella forsythia and Treponema denticola, respectively (Verdugo et al., 2015b). Different vulnerable populations might be at greater risk of herpesvirus-bacterial active infection or reactivation and, thus, prevalence rates may substantially fluctuate (Slots, 2010).

Gingival epithelial cells, from the junctional epithelium and sulcus, are commonly infected with EBV and may serve as important oral reservoirs of latent EBV-infected cells (Vincent-Bugnas et al., 2013). EBV has the ability to infect and establish a latent phase with a variety of cells, such as epithelial and endothelial cells, lymphocytes and neutrophils. However, when facing the innate immune response, the virus seems to be more prone to induce cellular apoptosis on over 75% of the surrounding neutrophils in less than 24 h post-EBV infection (Larochelle, Flamand, Gourde, Beauchamp, & Gosselin, 1998). Consequently, after down-regulating and disrupting the local immune response, an overgrowth of periodontopathic bacteria and yeast could potentiate peri-implant tissue breakdown.

3.2. Ability/inability to disrupt the peri-implant submucosal biofilm and maintain health

In an attempt to eliminate pathogenic biofilms around peri-implantitis lesions and to decontaminate the implant surface allowing for the re-establishment of an inflammation-free environment (Mellado-Valero, Buitrago-Vera, Solá-Ruiz, & Ferrer-García, 2013), open flap surgical access has gained momentum (Esposito et al., 2012; Lindhe et al., 2008; Heitz-Mayfield et al., 2012).

Non-surgical mechanical therapy, using curettes or ultrasonic devices in peri-implantitis lesions, has been shown to be ineffective in reducing bacterial counts at six months (Persson, Samuelsson, Lindahl, & Renvert, 2010b) and would possibly have parallel effects in virion reduction due to EBV's capacity to infect epithelial and endothelial cells from the implant biologic width. Nonetheless, when a surgical open flap approach was performed, mechanical therapy alone was able to significantly reduce bacterial counts at 3 months (Maximo et al., 2009).

Modern implants rough topography would explain the difficulty of achieving optimal surface degranulation and decontamination with or without surgical access. Unfortunately, current available scientific literature lacks long-term microbiological follow-up studies showing successful maintenance of peri-implantitis patients. Lack of follow-up and antibiotic susceptibility testing may leave specific ongoing microbial challenges difficult to eradicate, allowing peri-implantitis lesions to progress. Multiple documented clinical research have reported rapidly progressive, non-responsive to treatment peri-implantitis where broad-spectrum antibiotics were used (Rams et al., 2014a; Emrani et al., 2009; van Winkelhoff & Wolf, 2000; Leonhardt et al., 1999).

Implant surface characteristics seem to influence the progression of peri-implantitis lesions and bone loss due to the difficulty of achieving optimal surface decontamination. Today's modern implant surface area roughness values average approximately 2.0–2.5 μm pit. Superinfecting bacteria of the Enterobacteriaceae family, including, E. coli, Enterobacter aerogenes, Enterobacter cloacae, Salmonella enteritidis, Klebsiella pneumonia or Shigella dysenteriae, among others, are Gram negative facultative anaerobic rods, glucose fermenters and nitrate reducers, usually associated with intestinal, urinary and respiratory tract infections, but can be found in almost all natural habitats including the oral cavity. They have on average diameters of 0.5–1 μm and lengths of approximately 2 μm and have been found infecting implant and prosthetic devices (Sanders & Sanders, 1997; Choi et al., 2008; Naesens et al., 2009; Rams et al., 1996). These microorganisms are posed to flourish in years to come due to their ability to develop multidrug resistance to a number of broad-spectrum antibiotics such as beta-lactams, tetracyclines, aminoglycosides or even quinolones. Risks that can lead to the development of these superinfecting agents include, among other factors, prolonged hospital stay, immunosuppression, nail-biting, the use of contaminated toothbrushes or the presence of a foreign device such as an implant (Sanders & Sanders, 1997; Rams et al., 1990).

When left untreated, disease progression may be more pronounced on moderately rough surface area implants with Sa-values of 2.29 μm than on polished ones with Sa-values of 0.35 μm (Berglundh, Gottleibsd, Zitzmann, Lang, & Lindhe, 2007). The amount of bone loss after a period of plaque accumulation was significantly larger at implants with anodized surfaces (TiUnite®) than at implants with turned surfaces (Albouy, Abrahamsson, & Berglundh, 2012). The available scientific data suggest that the ability to eliminate the pathogenic biofilm from peri-implantitis lesions will be more compromised and difficult to achieve on rough implant surfaces (Charalampakis, Ramberg, Dahlén, Berglundh, & Abrahamsson, 2014). Scanning electron microscopy and microbiological analysis showed that the combination of mechanical and chemical cleansing failed to completely remove the bacterial biofilm from easily accessible titanium discs worn during 4 days by healthy individuals (Charalampakis et al., 2014).

At present, there is still no study proposing an effective, reliable methodology for treating peri-implant disease. Treatment interventions for peri-implantitis with follow-ups longer than one year have suggested disease recurrence in up to 100% of the treated individuals (Esposito et al., 2012). Due to the chronic nature of the disease and the difficulty to eradicate causative pathogens, re-treatment seems likely (Esposito et al., 2012).

As a result, maintaining healthy peri-implant tissues long-term might be an uncertain mission. Moreover, periodontal maintenance patients tend to harbor significantly higher levels of the red complex bacteria and long-term control of aggressive periodontopathic bacteria seems a difficult task to attain (Teles, Patel, Socransky, & Haffajee, 2008; Buchmann, Müller, Heinecke, & Lange, 2000).

A key aspect in both periodontitis and peri-implantitis patients is establishing a rigorous and personalized maintenance protocol assessing individual microbial profiles regularly to be able to monitor potential clinical changes and reduce risks.

3.3. Systemic antibiotics in the treatment of peri-implantitis (Tables 1 and 2)

Lack of clear guidelines from periodontitis studies and scarcity of scientific data from peri-implantitis research, on the use of systemic antibiotics, can translate into unsafe science-based
clinical decisions. Few peri-implantitis studies have evaluated their use in humans and only one case series study has reported clinical and microbiological results up to five years (Leonhardt, Dahlén, & Renvert, 2003). A recent study showed that the additional use of systemic antibiotics did not have a significant clinical impact on the treatment of peri-implant mucositis at 6 months as compared to non-surgical debridement alone (Hallström, Persson, Lindgren, Olofsson, & Renvert, 2012). Arguably, the selection of the antibiotic, dosage and duration could have possibly yielded different outcomes. Conversely, a trend for improved clinical and microbiological results could be observed in individuals with severe periodontitis taking metronidazole and amoxicillin for 14 days instead of the usual 7-day protocol (Feres, Figueiredo, Soares, & Faveri, 2015). Nonetheless, these data need substantiation.

Extensive surgical and individualized systemic antimicrobial therapy has been shown to be insufficient in maintaining pathogen-free peri-implant tissues over a five-year period (Leonhardt et al., 2003). In one study, implants were decontaminated using 10% hydrogen peroxide followed by sterile saline irrigation, and patients rinsed with 0.2% chlorhexidine twice/day for two weeks after surgery. Periodontopathic bacteria were still present in 8 out of the 9 treated patients or 53% of the affected sites (Leonhardt et al., 2003). Microbiological parameters did not improve by increasing the antibiotic regime to 4 weeks, re-treatment was necessary, and 27% of the study implants were lost.

<table>
<thead>
<tr>
<th>Study &amp; follow-up</th>
<th>Protocol</th>
<th>Outcome</th>
<th>Implant system</th>
<th>Author/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human 1-year with microbiological follow-up N = 9 patients</td>
<td>Non-surgical mechanical therapy + 0.5% CHX irrigation + 1 g/day/10 days systemic metronidazole + home pocket 0.2% CHX irrigation</td>
<td>Immediate anaerobic load reduction &amp; clinical improvement. At 9 months G- anaerobic rods % up 36% vs. the 42% at pretreatment; G+ anaerobic rods increased from 8.42% to 15.6% at 1 year</td>
<td>Titanium hollow cylinder (Straumann)</td>
<td>Mombelli &amp; Lang (1992)</td>
</tr>
<tr>
<td>Human 5-year with microbiological follow-up N = 9 patients</td>
<td>Surgical debridement: decontamination with 10% hydrogen peroxide + saline solution. Postop 0.2% CHX rinse 2 weeks + individualized systemic antibiotics based on susceptibility test (amoxicillin + metronidazole; tetracycline; clindamycin; ciprofloxacin) single daily dose for 2 or 4 weeks</td>
<td>Clinical, microbiological and radiographic evaluation: treatment success in 58% of implants treated Periodontopathic bacteria still present in 8 out of the 9 treated patients (53% of sites); Re-treatment necessary: 27% of the study implants lost; the rest unchanged/gain or continue to lose bone. No control microbiol outcomes.</td>
<td>Bränemark System (Nobel Biocare)</td>
<td>Leonhardt et al. (2003)</td>
</tr>
<tr>
<td>Human 1-year No microbiological testing N = 24 patients</td>
<td>Surgical access + titanium/carbon fiber curettes + irrigation with sterile saline + gauze soaked in sterile saline. Systemic antibiotics: 7 days amoxicillin + metronidazole + 0.20% CHX rinse 4 weeks</td>
<td>Clinical and radiological parameters improved after 3 months for up to 12 months; 88% of patients (92% of implants) with stable crestal bone levels or bone gain at twelve months but only 47% of the implants had complete resolution of bleeding on probing; ongoing bone loss at 12 months in a sub-group of 3 patients; side effects mostly gastrointestinal in 25%</td>
<td>Bränemark turned = 5 Straumann TPS = 3 Astra TiOblast = 2 Anodized TitInite Nobel Biocare = 9 Straumann SLA = 11 Acid-etched Entegra/ Sybron = 1 Plasma-sprayed Frialt-2, Dentiply = 2 HA coating, Calcitek = 3</td>
<td>Heitz-Mayfield et al. (2012)</td>
</tr>
<tr>
<td>Human 2-year No microbiological testing N = 31 patients</td>
<td>Resective surgical therapy + osseous re-contouring, implant surface debridement and decontamination with CHX irrigation and apically re-positioned flaps; 300 mg clindamycin TID 1 week, +0.12% CHX rinse twice/day/2 weeks</td>
<td>From 31 patients, only 48% had no disease signs; 24 (77%) with no pockets ≥6 mm and BOP/suppuration; Implants with greater severe bone loss and pockets ≥5 mm at baseline more likely to present peri-implant disease at follow-up</td>
<td>IMZ &amp; M2, Friadent</td>
<td>Khoury &amp; Buchmann (2001)</td>
</tr>
<tr>
<td>Human 3-year Microbiological testing only at baseline N = 25 patients</td>
<td>Surgical access &amp; autogenous bone grafting &amp; systemic antibiotics administered following baseline microbiol susceptibility test: 1 week; sites treated with no membranes or non-resorbable and resorbable membranes</td>
<td>Dehiscence, fistula formation &amp; osseous sequestrum strongly associated with use of membranes 60% of time; None of the autogenous-only treated sites (without membrane) developed such complications</td>
<td>Bränemark turned = 122 Straumann TPS = 40 Astra = 6</td>
<td>Serino &amp; Turri (2011)</td>
</tr>
<tr>
<td>Human 1–5 year No microbiological testing N = 36 patients at 1 year N = 25 at 5 years</td>
<td>Surgical access &amp; bone substitute (allogene derived) used to fill peri-implant defects with &amp; without resorbable membranes. Implant decontaminated with 3% H₂O₂ and rinsed with saline; systemic antibiotics for 10 days starting day before surgery: amoxicillin (375 mg TID) + metronidazole (400 mg BID) or clindamycin (300 mg BID) Post-op rinsing 0.1% CHX for 5 weeks</td>
<td>60% of study patients were smokers; bleeding found at 1 year in 22–25% of treated implants both groups. Frequent membrane exposure at 2 weeks in 43.8% of implants and at 7 weeks (34.4%) At 5y follow-up, sites treated with bone substitute + membrane showed increased plaque index of 31.5% &amp; bone loss vs. sites treated with bone substitute only Radiographic defect fill averaged 1.1–1.3 mm No change or loss of bone in 40% of study patients (10/25), 3-month supportive therapy on all patients for 5 years.</td>
<td>Bränemark turned</td>
<td>Roos-Jansäker et al., (2007); Roos-Jansäker et al., (2014)</td>
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CHX: chlorhexidine; BOP: bleeding on probing; TID: three times/day; BID: two times/day; TPS: titanium plasma sprayed; SLA: sand-blasted, large-grit, acid-etched.
or continued to lose bone during the 5-year follow-up (Leonhardt et al., 2003). However, microbiological culture monitoring and antibiotic susceptibility testing may have prevented the rise of implant superinfections in susceptible individuals harboring enteric rods, including E. coli and E. cloacae, and A. actinomyctecomitans at baseline (Leonhardt et al., 2003).

Non-surgical mechanical debridement, local chlorhexidine irrigation and systemic ornidazole (1 g/day/10days) yielded immediate improved clinical and microbiological parameters at 10 days in a group of nine peri-implantitis patients (Mombelli & Lang, 1992). The authors noted a shift back towards baseline values of proportions of Gram-negative anaerobic and facultative rods that eventually improved again by the end of the 12-month follow-up. However, at nine months the proportions of these pathogens combined were up 36% as compared to the pretreatment values of 42.5% (Mombelli & Lang, 1992). For Gram-positive anaerobic and facultative rods, the combined percentages at the end of the 12 months were significantly higher than pretreatment levels, 15.6% versus 8.4% (Mombelli & Lang, 1992).

Surgical access, for mechanical removal of inflamed granulation tissue and saline implant surface decontamination, coupled with empiric systemic antibiotics (500 mg amoxicillin + 400 mg metronidazole 3 times/day/7 days), has been shown to improve clinical parameters (pocket reduction, bleeding and suppuration) in a group of 24 peri-implantitis patients (Heitz-Mayfield et al., 2012).

Patients were also instructed to rinse with 0.2% chlorhexidine twice a day for 4 weeks after surgery and monitored weekly the first month and every 3 months thereafter without microbiological evaluation throughout the study (Heitz-Mayfield et al., 2012). The aforementioned non-randomized cohort multi-center study reported 88% of the patients (92% of implants) having stable crestal bone levels or bone gain at twelve months but only 47% of the implants had complete resolution of bleeding on probing. Three study patients continued to show ongoing bone loss at the 12-month follow-up (Heitz-Mayfield et al., 2012). The use of systemic amoxicillin and metronidazole was also associated with adverse effects mostly related to gastrointestinal disturbances in 25% of the study population (Heitz-Mayfield et al., 2012). The oropharyngeal as well as intestinal ecological balance can be disturbed after administration of systemic antibiotics, favoring the overgrowth of opportunistic pathogens (Sullivan et al., 2001; Rashid, Weintraub, & Nord, 2012).

A two year follow-up study reported that resective surgical therapy with osseous re-contouring, implant surface debridement and decontamination with chlorhexidine irrigation and apically re-positioned flaps yielded 15 out of the 31 study patients (48%) with no signs of disease and 24 (77%) with no pockets >6 mm and BOP/suppuration (Serino & Turri, 2011). Implants with greater severe bone loss and pockets >5 mm at baseline were more likely to present with peri-implant disease at follow-up. Patients took 300 mg of clindamycin three times a day for one week, starting the day before surgery and were instructed to rinse with 0.12% chlorhexidine twice a day for 2 weeks (Serino & Turri, 2011).

A different surgical peri-implantitis approach combining autogenous bone grafting and systemic antibiotics on 25 patients has shown controversial results depending on whether membranes were used or not for guided bone regeneration (Khoury & Buchmann, 2001). Antibiotics were administered according to a microbiology susceptibility test performed on each individual at baseline and were taken for one week starting the day before surgery as well as 0.2% chlorhexidine rinse twice/day. After degranulation, peri-implant defects were irrigated with 0.2% chlorhexidine, citric acid (pH 1) applied for one minute onto the implant surface and then rinsed with hydrogen peroxide and 0.9% saline. Healing complications including dehiscence, fistula formation and osseous sequestrum, were strongly associated with the use of membranes (resorbable & non-resorbable) 60% of the time. Seventeen out of the 29 membrane treated implants sites developed early post-operative complications regardless of systemic antibiotics administration (Khoury & Buchmann, 2001). In contrast, none of the autogenous-only treated sites (without membrane) developed such complications and probing depths averaged 3 mm at the three-year follow-up (Khoury & Buchmann, 2001).

The use of an algae-derived calcified grafting material has been used to fill peri-implant defects in a group of 36 patients with and without resorbable membranes. Implants were decontaminated with 3% hydrogen peroxide and rinsed with saline, and systemic antibiotics were administered for 10 days starting the day before surgery, amoxicillin (375 mg TID) + metronidazole (400 mg BID) or clindamycin (300 mg BID). Post-op rinsing with 0.1% chlorhexidine lasted 5 weeks. No microbiological analysis was performed. The majority of patients (60%) were smokers and the reported bleeding was found at one year in approximately 22–25% of the treated

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**Table 2**

Scores of quality assessment for prospective studies: 12-point MINORS scale.

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<td>Clear stated aim</td>
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<td>2</td>
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<td>Inclusion of consecutive patients</td>
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<tr>
<td>Prospective collection of data</td>
<td>2</td>
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Score 0 (not reported), 1 (reported but inadequate) and 2 (reported and adequate).
implants for both groups. Membrane exposure occurred frequently at 2 weeks in 43.8% of the treated implants and at 7 weeks (34.4%) (Roos-Jansäker et al., 2007). A 5-year follow-up on the same group of patients (n = 25) showed that sites treated with the bone substitute + membrane had increased bone loss and plaque index (31.5%) versus sites using bone substitute alone. Radiographic defect fill averaged 1.1–1.3 mm and no change or loss of bone was observed in 40% (10/25) of the twenty-five study individuals. Patients followed a personalized 3-month supportive therapy that allowed maintenance of good plaque control levels (Roos-Jansäker et al., 2014).

A short 3-month peri-implantitis study evaluating surgical mechanical therapy without systemic antimicrobials has shown significant reductions in probing depths, bleeding on probing and bacterial counts (Máximo et al., 2009). Implants were scaled with Teflon curettes and decontaminated using an abrasive sodium carbonate air-power system. Patients were instructed to rinse twice a day with 0.12% chlorhexidine for one week. Resolution of inflammation was not successful in 45% of the treated implants and the main pathogenic species detected at baseline, F. gingivalis, T. denticola, T. forsythia and Purvimonas micra, were still present at the end of the 3 month follow-up (Máximo et al., 2009).

### 3.4. Surgical treatment of peri-implantitis without systemic antibiotics (Table 3)

Resective surgical therapy with osseous re-contouring, implant surface debridement and decontamination, and apically re-positioned flaps has been shown to improve clinical parameters in a group of 30 individuals, however, complete resolution of inflammation was almost never achieved at twelve months (De Waal, Raghoebar, Huddleston Slater, Meijer, Winkel, & van Winkelhoff, 2013). The authors noted greater immediate anaerobic bacterial reduction using 0.12% chlorhexidine for decontamination than the placebo solution (saline) but without superior clinical or radiological results at one year (De Waal et al., 2013). Sixty-six out of the 69 implants present at one year showed at least one site with bleeding on probing and 15 implants with additional suppuration. Treatment was only successful (residual pockets <5 mm with no bleeding and/or suppuration) for 11 patients (38%) and 38 implants (49%) (De Waal et al., 2013).

A different 6 month study starting with 32 patients and then followed for 4 years in 17 individuals reported no significant impact of the method of surface decontamination, using Er:Yag laser vs. plastic curets and cotton pellets/sterile saline, on the

#### Table 3

<table>
<thead>
<tr>
<th>Study &amp; follow-up</th>
<th>Protocol</th>
<th>Outcome</th>
<th>Implant system</th>
<th>Author/ Year</th>
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<tr>
<td>Human 1-year Microbiological testing at baseline only intra-surgical (pre &amp; post decontamination) N = 30 patients</td>
<td>Resective surgical therapy + apically re-positioned flaps; debridement &amp; 0.12% CHX vs. saline decontamination; 2 week rinse/2times/day 0.12% CHX + 0.05% CPC without alcohol</td>
<td>Complete resolution of inflammation almost never achieved for both groups. Greater immediate anaerobic reduction with 0.12% CHX vs. saline decontamination but without superior clinical or radiological results at 1y. Treatment only successful (residual pockets &lt;5 mm with no bleeding and/or suppuration) for 11 patients (38%) and 38 implants (49%)</td>
<td>Bränemark turned Anodized TiUnite Nobel Biocare Straumann TPS, SLA, SLA active Astra TiOblast Osseospeed IMZ Titanium plasma-sprayed Grit-blasted acid-etched Friadent plus, Dentsply Astra nanotype surface</td>
<td>De Waal et al. (2013)</td>
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<tr>
<td>Human 4-year No microbiological testing N = 17 patients</td>
<td>Surgical debridement: surface decontamination Er:Yag laser vs. plastic curets + cotton pellets/sterile saline + implantoplasty; defects grafted with a bovine graft &amp; resorbable porcine membrane; postop rinse 0.2%CHX twice/day/2 weeks</td>
<td>Probing depth reductions accounted to 1.3 and 1.2 mm and bleeding on probing to 23.5% and 14.8% for both groups, respectively. Due to suppuration and progressive bone loss 4 patients discontinue the study</td>
<td>Bränemark turned Camlog Straumann, microrough surface KSI machine Nobel replace, microrough surface Tapered Screw Vent, Zimmer, microrough surface Xive, Dentsply Friadent, microrough surface</td>
<td>Schwarz et al. (2013)</td>
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<td>Human 5-year No microbiological testing N = 32 patients</td>
<td>Surgical access + decontamination with conventional debridement vs. CO2 laser. Defects grafted with beta-TCP + autogenous bone (50:50) or left alone. Implants receiving grafts were screw retained only &amp; covered with a non-resorbable Gore-Tex membrane &amp; submerged 4 months</td>
<td>A total of 13 implants (18%) removed. Inflammation reduced initially but increased again by the end of the study in every group No long-term differences between the two protocols</td>
<td>IMZ Frialit-2, Friadent Bränemark turned Straumann</td>
<td>Deppe et al. (2007)</td>
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clinical outcomes after surgical treatment of advanced peri-implantitis lesions (Schwarz, Sahm, Ighlaut, & Becker, 2011; Schwarz, Hegewald, John, Sahm, & Becker, 2013). Probing depths reduced by 1.3 and 1.2 mm and bleeding on probing reduced to 23.5% and 14.8% for both groups, respectively. Implantoplasty was performed on all affected implants and bony defects grafted with a bovine material. Due to suppuration and progressive bone loss four patients had to discontinue the study. The authors advised that the long-term clinical stability could be influenced by factors other than the method of surface decontamination (Schwarz et al., 2011).

A 5-year clinical report on 32 patients with 73 ailing implants compared the effects of decontamination using either conventional debridement or CO2 laser. Defects were either grafted with beta-tricalcium phosphate + autogenous bone (50:50 ratio) or left alone (Deppe, Horch, & Neff, 2007). Implants were covered with a non-resorbable Gore-Tex membrane and submerged. Complications of edema and severe and chronic infection, resulted in implant loss. A total of 13 implants (18%) were removed. Inflammation was reduced initially but increased again by the end of the study in every group. No microbiological or antibiotic susceptibility testing was performed. Although CO2 laser may be more efficacious in deep, narrow bony defects, than conventional debridement, the authors concluded that there were no differences in the long-term decontamination effects between the two protocols (Deppe et al., 2007).

3.5. Summary of systematic review

For those few studies reporting microbiological data at follow-up, risk was defined as the persistence of specific periodontopathic bacteria at follow-up. Additionally, for those studies that did not report such data, risk was evaluated as persistence of inflammation, bleeding, suppuration and progressive bone loss or implant loss (Table 1).

The only two studies (Leonhardt et al., 2003; Mombelli & Lang, 1992) with microbial follow-up have demonstrated that, after surgical and non-surgical therapy with systemic antimicrobials, opportunistic periodontopathic bacteria (enteric rods, E. coli and E. cloacae, A. actinomycetemcomitans, P. gingivalis) can reappear after a period of time. Increasing the antibiotic regime to four weeks is unlikely to prevent specific bacterial overgrowth either and re-treatment may become necessary (Leonhardt et al., 2003).

Additionally, a combination of amoxicillin and metronidazole for seven days has shown that only 47% of the treated implants had complete resolution of bleeding on probing at one year, with ongoing bone loss in three patients and gastrointestinal disturbances in 25% of the total of 24 individuals treated (Heitz-Mayfield et al., 2012). Similarly, a group of 31 peri-implantitis individuals showed only 48% with no signs of the disease (Serino & Turri, 2011). Thus, a strict personalized supportive maintenance therapy may become critical in preventing disease recurrence, primarily, to keep the proportions of unwanted pathogens low and help sustain a normal ecological balance. A recent five-year follow-up study has shown the benefits of a 3-month recall program. Low bleeding scores and no change or loss of bone in 10 out of the 25 study individuals was reported (Roos-Jansäker et al., 2014).

Altogether, the existing limited scientific data suggests that the use of systemic antimicrobials to treat peri-implantitis will not help generate stable long-term outcomes and could allow the overgrowth of superinfecting microorganisms. Opportunistic pathogens, such as S. aureus or EBV, may favor the conversion of a normal symbiotic ecosystem into a dysbiotic ecosystem by down-regulating the local innate immune response, thus, allowing the overgrowth of superinfecting bacteria and yeast. Moreover, the emergence of antimicrobial resistance coupled with indiscriminative antibiotic administration could support the escalation of peri-implant disease in years to come. Identifying opportunistic microorganisms, by means of microbial sampling, is essential to preventing superinfections. If systemic antibiotics are deemed necessary, an antimicrobial susceptibility test should be performed to minimize risks.

4. Discussion

The present review on risks associated with the use of systemic antibiotics in peri-implantitis treatment illustrates the importance of adequate clinical and microbiological follow-up, microbiological susceptibility testing and non-empiric antimicrobial regimens (Rams et al., 2014a; Rams et al., 2014b; Helovuo et al., 1993; Rams et al., 1990; Teles et al., 2008; Buchmann et al., 2000; Leonhardt et al., 2003). Thus far, there has been little documentation of the potentially deleterious effects of broad-spectrum systemic antibiotics use in peri-implant disease therapy.

This is due to the lack of studies with long-term microbiological follow-up. The development of chronic peri-implant and periodontal superinfections is a complication that may initially be overlooked but could lead to sustained progressive bone loss compromising dental implant outcomes (Emrani et al., 2009; van Winkelhoff & Wolf, 2000; Teles et al., 2008; Buchmann et al., 2000; Leonhardt et al., 2003; Botero, González, Mercado, Olave, & Contreras, 2005). The deficiency of clear guidelines from periodontitis studies and paucity of scientific data from peri-implantitis research, on the use of systemic antibiotics, can lead to unsafe science-based clinical decisions.

With an estimated twelve million implants being placed annually worldwide, peri-implant bone loss has become, in the last few years, a complication difficult to resolve (Esposito et al., 2012; Albrektsson et al., 2014). Factors such as excess of cement or poorly fabricated implants handled by unqualified clinicians can worsen the prognosis and accelerate the progression of bone loss (Albrektsson et al., 2014; Qian et al., 2012; Wilson, 2009).

Clinically, the acknowledged and long-established risk factors for periodontitis may be considered as equivalent to those for peri-implantitis. Patients susceptible to periodontitis appear to be more vulnerable to peri-implantitis than those without a history of the disease (Heitz-Mayfield & Lang, 2010). Regardless of the initiating etiological factors, the disease process is exacerbated and maintained by specific microbial infection with bacteria and possibly yeasts and viruses (Rams et al., 2014a; Verdugo et al., 2015a; Verdugo et al., 2015b; Leonhardt et al., 1999; Heitz-Mayfield & Lang, 2010). Therefore, many clinicians have chosen to treat peri-implantitis as an infectious disease using broad-spectrum antibiotics (Heitz-Mayfield et al., 2012; Emrani et al., 2009; van Winkelhoff & Wolf, 2000; Leonhardt et al., 2003; Mombelli & Lang, 1992; Serino & Turri, 2011; Khoury & Buchmann, 2001; Roos-Jansäker et al., 2007). Unfortunately, though systemic antimicrobials have shown to improve therapy outcomes in aggressive periodontitis individuals (Sgołastra, Petrucci, Gatto, & Monaco, 2012), time and indiscriminating empiric regimens have made the risk of antibiotic resistance development a reality (Rams et al., 2014a, 2014b; Poveda Roda, Bagan, Sanchis Bielsa, & Carbonell Pastor, 2007).

The present review shows that every clinical study claiming more or less successful therapy outcomes after treating peri-implantitis had, at follow-up, a sub-group of implants with either persistent inflammation, residual pockets, suppuration, progressive bone loss or implants that had to be removed (Table 1). Most clinicians performing grafting procedures, such as, guided bone regeneration to treat peri-implant defects, use antibiotics to avoid infectious complications and membrane contamination (Khoury & Buchmann, 2001; Roos-Jansäker et al., 2007). Yet still, the rate of infectious complications was significant, between 44 and 60%. The
estimated risk of contamination and infection in these circumstances can be high due to the difficulty of eliminating 100% of the pathogenic biofilm from the contaminated rough implant surface. Moreover, the typical patient population treated are likely susceptible hosts with a past history of periodontitis, and most clinicians do not perform a baseline and follow-up microbial sampling (Heitz-Mayfield et al., 2012; Serino & Turri, 2011; Roos-Jansäker et al., 2007; Roos-Jansäker et al., 2014; De Waal et al., 2013; Schwarz et al., 2011; Schwarz et al., 2013; Deppe et al., 2007).

To reduce the risks of microbial recontamination in these susceptible populations, personalized periodontal supportive therapy might help prevent complications and peri-implantitis relapses. A 3-month recall protocol has shown positive outcomes at five years in a small group of smoker patients with a past history of periodontal disease (Roos-Jansäker et al., 2007).

It is plausible to speculate that the rapid progression of bone loss in some studies or the persistent inflammation of others was due to infection with superinfecting agents resistant to antimicrobials (Rams et al., 2014a; Verdugo et al., 2015b; Emrani et al., 2009; van Winkelhoff & Wolf, 2000; Leonhardt et al., 1999; Vincent-Bugas et al., 2013; Slots, 2010; Leonhardt et al., 2003; Botero et al., 2005; Heitz-Mayfield & Lang, 2010). Previous studies have identified superinfecting agents, colonized in the peri-implant submucosa, displaying a remarkable antimicrobial resistance (Rams et al., 2014a; Emrani et al., 2009; van Winkelhoff & Wolf, 2000; Helovuo et al., 1993; Leonhardt et al., 2003; Heitz-Mayfield & Lang, 2010). As a result, Candida and Staphylococcus spp., and enteric rods, among others, have been frequently isolated from peri-implantitis lesions (Leonhardt et al., 1999; Leonhardt et al., 2003). Microbiological culture monitoring and antibiotic susceptibility testing could prevent the emergence of implant superinfections in susceptible individuals harboring microorganisms such as E. coli and E. cloacae at baseline (Leonhardt et al., 2003).

The individual human indigenous microbiota or normal microflora is fairly constant at each ecological habitat (Sullivan et al., 2001). The normal human microflora acts as a barrier against colonization by opportunistic microorganisms or overgrowth of already present pathogens like yeasts, Clostridium difficile, or enteric rods. Overgrowth control of opportunistic pathogens, also called colonization resistance, is maintained not only by the normal indigenous microflora, but also by different physiological factors such as secretion of saliva and gastric acid (Sullivan et al., 2001; Rashid et al., 2012). If we could use only antimicrobials that do not alter colonization resistance, then the risk of development and spread of resistant strains among patients, and dissemination of resistant elements between pathogens, would be minimized (Rashid et al., 2012).

C. albicans may be particularly difficult to eradicate due to its capacity to invade host tissues, form hyphae, and ability to interact with commensal bacteria to synergistically stimulate its virulence (Martin et al., 2011; Xu et al., 2014). Quick antimicrobial therapy should be delivered when a clinical or subclinical candidiasis is detected. Prolonged C. albicans infection could induce chronic tissue destruction through pro-inflammatory cytokine up-regulation (Xu et al., 2014; Dongari-Bagtzoglou et al., 2004). This cytolytic activity could trigger interleukin IL-1alpha release from yeast-infected oral epithelial cells, increasing cytokine secretion from uninfected epithelial cells, and thus creating a vicious cycle (Dongari-Bagtzoglou et al., 2004).

The genera of the enterobacteraeaceae, a family of Gram-negative facultative anaerobic rod-shaped bacteria, are among the most pathogenic and commonly found microorganisms in clinical microbiology (Sanders & Sanders, 1987). Risks that can lead to the development of these superinfecting agents include, among other factors, prolonged hospital stay, immunosuppression, nailing, use of contaminated toothbrushes and the presence of a foreign device such as an implant (Sanders & Sanders, 1997; Bayda et al., 2007; Bezirtzoglou et al., 2008). Enterobacter species also have a reputation for their ability to develop multidrug resistance to a number of broad-spectrum antibiotics such as beta-lactam antibiotics, tetracycline, aminoglycosides or even quinolones (Sanders & Sanders, 1997; Choi et al., 2008; Naesens et al., 2009).

Combination antibiotic regimens of amoxicillin and metronidazole for 7 days have yielded significant qualitative and quantitative alterations in the normal human indigenous microflora, and generated shifts from susceptible to resistant strains and overgrowth of yeast and resistant enterobacteraeaceae with persistence of resistant strains 4 weeks after administration (Adamsson, Nord, Lundquist, Sjöstedt, & Edlund, 1999). Heitz-Mayfield et al. (2012) reported in their study that the use of systemic amoxicillin and metronidazole was associated with gastrointestinal disturbances in 25% of the study population. They also reported that, despite 92% of implants showing stable crestal bone levels, only 47% of the treated implants had complete resolution of bleeding on probing and three patients, out of 24 peri-implantitis individuals, continued to show ongoing bone loss at the 12-month follow-up. No microbiological evaluation was performed (Heitz-Mayfield et al., 2012). In contrast, microbiological monitoring and antibiotic susceptibility testing prevented the emergence of implant superinfections in susceptible patients harboring enteric rods and A. actinomycescomitans at baseline, and yet, pathogenic bacteria were still present in 53% of the affected sites at five years (Leonhardt et al., 2003). Changing the antibiotic regime to 4 weeks did not improve the microbiological parameters, re-treatment was often necessary, and 27% of the study implants were lost or continued to lose bone during the 5-year follow-up (Leonhardt et al., 2003).

The mixed microbiota of peri-implantitis lesions resembles somehow that of periodontal infections, but with some significant differences. The peri-implant and periodontal microbiomes represent microbiologically distinct ecosystems. A significant difference is the frequent presence of higher proportions of staphylococci and enteric bacteria in peri-implantitis lesions (Belibasakis, 2014; Charalampakis & Belibasakis, 2015). The microbial diversity infecting peri-implantitis lesions versus healthy implants is complex and could harbor well over 40 different genera per sample of mostly Gram negative and positive anaerobic opportunistic pathogens and Epstein-Barr virus (Kumar, Mason, Brooker, & O’Brien, 2012; da Silva et al., 2014; Rakic, Grusovin, & Canullo, 2015). Pyrosequencing and Sanger sequencing technology have allowed to identifying large arrays of bacteria infecting peri-implantitis lesions and have shown distinct differences between health and disease. Peri-implantitis seems to be a more microbiologically heterogeneous infection with primarily Gram-negative species and less complex microbiota than periodontitis (Kumar et al., 2012). Considering the average sizes of 0.5–2 μm for most superinfecting bacteria, such as, Enterobacter or Staphylococcus species, and the matching rough implant surfaces micro pits, successful pathogen eradication seems a questionable quest (Charalampakis et al., 2014). Moderately rough implant surfaces would likely favor the thriving of superinfecting agents after empiric antibiotic regimens. The combination of mechanical and chemical decontamination, in healthy subjects, has failed to eradicate bacterial biofilms from easily accessible titanium discs after only a short 4-day exposure (Charalampakis et al., 2014).

The presence of EBV seems more likely at peri-implantitis lesions than healthy implants and even saliva for the same individual (Verdugo et al., 2015b) Epstein-Barr virus, as a potential superinfecting agent, can complicate therapy outcomes due to its capacity to block local neutrophil innate response, affect/infect endothelial cells and damage implant biologic width (Vincent-
Bugnás et al., 2013; Kato et al., 2013; Larochelle et al., 1998; Farina et al., 2014; Savard & Gosselin, 2006). Successful treatment of EBV-associated severe periodontitis using valacyclovir 500 mg/day for 10 days has been documented (Sunde, Olsen, Enersten, & Grinde, 2008). Therefore, antiviral therapy could be considered in future research protocols for EBV-associated peri-implantitis. Elimination of herpesviruses from periodontal and peri-implant sites may improve individual oral health status and reduce the frequency of herpesvirus viremia and salivary transmission, possibly lowering the risk of serious medical diseases and disabilities (Slots, 2015).

A key aspect in peri-implantitis would be to establish precise and personalized maintenance protocols, eliminate reservoirs of pathogenic bacteria, particularly on those with past history of periodontitis (Roos-Jansäker et al., 2014; Van Winkelhoff, 2012), and frequently evaluate individual microbial profiles so that early clinical changes can be monitored and potential risks reduced. It is well documented that superinfecting agents, such as, Enterobacter, Candida, or Staphylococcus species, can significantly thrive after the administration of systemic antibiotics (Sullivan et al., 2001; Helovuo et al., 1993; Rashid et al., 2012; Adamsson et al., 1999). Systemic antimicrobials can negatively affect the protective oropharyngeal microflora by altering the delicate ecological balance and favoring the overgrowth of opportunistic pathogens (Sullivan et al., 2001; Rashid et al., 2012; Adamsson et al., 1999).

The increased use of dental implants worldwide coupled with the upraise of antimicrobial resistance and indiscriminate antibiotic administration, is likely to support the escalation of peri-implant disease in years to come, with an already estimated prevalence of nearly 56% (Lindhe et al., 2008).

An effort should be made to monitor and revise patients’ medical history regularly, tracking past antibiotic use, smoking habits and diabetes status, among other conditions, and consider the use of probiotics to protect the normal microflora, in order to help prevent peri-implant superinfection emergence. Further studies, particularly randomized clinical trials, are urgently needed to develop effective antimicrobial and maintenance protocols in peri-implantitis patients, to identify individuals at risk, and to understand the potential role of superinfecting pathogens in the progression of peri-implant bone loss.

5. Conclusion

There is no proven effective treatment protocol to maintain peri-implantitis patients free of inflammation long-term. Peri-implant superinfections are a potential risk associated with broad-spectrum antibiotics in immunocompetent individuals. Non-responsive to treatment peri-implantitis lesions, associated with rapidly progressive bone loss, are possibly induced and aggravated by superinfecting agents. Lack of follow-up, antibiotic susceptibility testing, and indiscriminate empiric treatment regimens may lead to specific ongoing microbial challenge that can exacerbate and maintain the disease progression. Personalized 3-month supportive therapy may help prevent risks by decreasing specific pathogen proportions and maintaining optimal plaque control.

Conflict of interest

None. All authors have read and approved the final article.

Author contribution

Each author performed the following tasks:

1. F. Verdugo: Inception of concept & study design; data collection/analysis & interpretation of collected scientific data; drafting of article; critical revision of article at all stages & final revision & approval. Accountable for all aspects of the work and will ensure that questions related to the accuracy or integrity of the study are appropriately investigated and resolved.

2. T. Laksmana: (1) Acquisition, analysis & interpretation of collected data; (2) critical revision of paper; (3) final revision and approval of paper; (4) agree to be accountable for all aspects of the work.

3. A. Uribarri: (1) Acquisition & analysis of scientific data; (2) critical revision of paper; (3) final revision and approval of paper; (4) agree to be accountable for all aspects of the work.

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