

# Gram-Negative Enteric Rods Associated to Early Implant Failure and Peri-Implantitis: Case Report and Systematic Literature Review

Bacilos Entéricos Gram-Negativos Asociados a Fracaso Temprano de Implantes y Peri-Implantitis: Reporte de un Caso y Revisión Sistemática de Literatura

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**ABSTRACT:** The microbiota associated with failed implants includes *Pseudomonas* and Gram-negative enteric rods. The present study reports a case of *Escherichia coli* associated to early implant failed that was resistant in vitro to doxycycline, amoxicillin, metronidazole, and clindamycin, but was susceptible in vitro to ciprofloxacin and aminoglycosides. The literature concerning the prevalence of the opportunistic microorganisms in early implant failure and peri-implantitis patients, and the usual treatment of these patients harboring *Pseudomonas* and enteric rods was also revised.

**KEY WORDS:** peri-implantitis, enteric rods, pseudomonas, implant failure.

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## INTRODUCTION

Peri-implantitis is understood to consequence in bone loss around the dental implants and succeeding damage of osseointegration (Mombelli *et al.*, 2012). The risk factors related to peri-implantitis involve smoking, occlusal or parafunctional forces, premature loading, ill-directed stress, periodontitis or microbial infection (Heitz-Mayfield *et al.*, 2014). An early implant failure or impaired healing corresponds to the inability to establish osseointegration. Early failure can be produced by diverse reasons, e.g. traumatic surgery, overheating during drilling and microbial infection (Quirynen *et al.*, 2002).

Certain implants appear to be more at risk for occlusal overload, whereas other systems are more disposed to plaque build-up. On the other hand, implants in partially edentulous patients, in contrast to fully edentulous subjects, will easily be colonized by putative periodontal pathogens (Quirynen *et al.*)

The microbiota associated with failed implants has been described previously. Assumed periodontopathic microorganisms identified by culture

encompassed *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Peptostreptococcus micros*, *Campylobacter rectus*, *Fusobacterium* species, *Prevotella intermedia*; moreover yeasts, spirochetes, *Pseudomonas* (Albertini *et al.*, 2015; Alcoforado *et al.*, 1991; Botero *et al.*, 2005; Consuegra *et al.*, 2011; Persson & Renvert, 2013; Rosenberg *et al.*, 1991) and Gram-negative enteric rods (Rams *et al.*, 2014; Tabanella *et al.*, 2009; Listgarten & Lai, 1999; Leonhardt *et al.*, 1999, 2003; Mombelli *et al.*, 1987) have been also recognized.

Enteric microorganisms and *Pseudomonas* are opportunistic pathogens in an extensive variety of human infections and they can be identified in the subgingival location of periodontitis patients (Gupta, 2002; Slots *et al.*, 1990). These microorganisms are capable of generating virulence factors and have the ability to occupy human tissue. Subgingival enteric rods frequently persevere following periodontal debridement and surgery and have been considered as strategic pathogens in cases of refractory periodontitis. Furthermore, they display less susceptibility to

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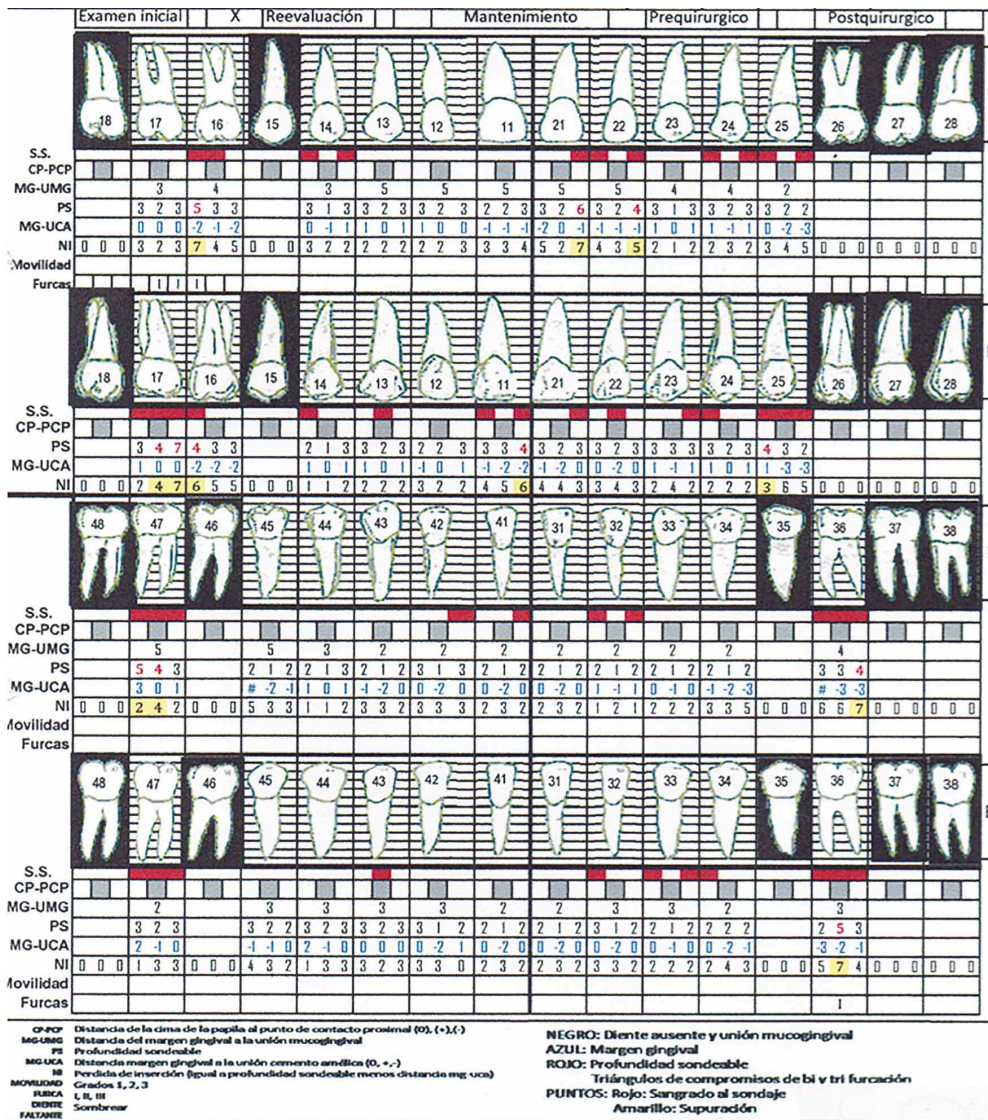
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chlorhexidine and the information that these microorganisms demonstrate in vitro resistance to the majority of adjunctive antibiotics used to treat periodontitis, means that periodontal infections associated with these organisms do not respond to conventional management modalities (Slots *et al.*).

The current article aimed to report a case of a Gram-negative enteric rod-associated to early implant failure and to review the literature concerning the prevalence of opportunist microorganism in early implant failure and peri-implantitis patients; the usual treatment of peri-implantitis patients harboring enteric rods also was revised.

### CASE REPORT

On August 2012 a 52-year-old nonsmoking female patient, with no systemic condition with antecedents of localized chronic periodontitis (Fig. 1) presented to the School of Dentistry of the Universidad de Antioquia, Medellín, Colombia. A medical history and clinical and radiographic examination (Fig. 2) were conducted. Probing depth, recessions, clinical attachment loss, full-mouth bleeding on probing and full-mouth dichotomous plaque scores were determined (Fig. 1). The diagnosis of chronic periodontitis was made based on criteria defined previously (Page & Eke,



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Fig. 1. Periodontal examination showing localized chronic periodontitis.



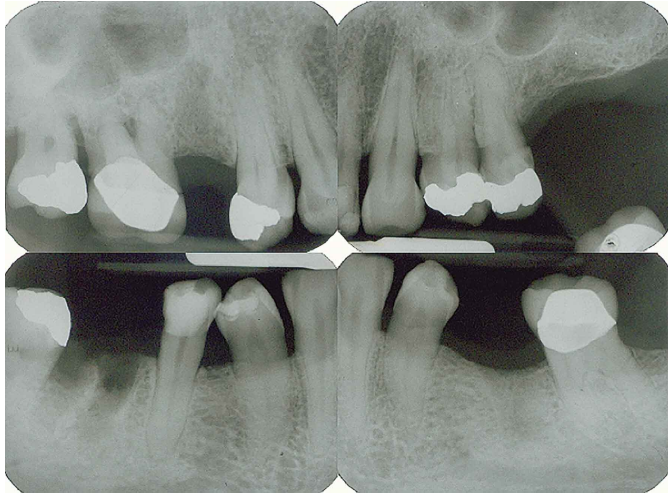


Fig. 2. Radiographic record before implant position.

2007). Subsequently, the periodontal therapy was planned and a detailed informed consent was obtained. As a record of her dental history, the patient had a radiograph taken on 2011. The radiograph revealed her periodontal condition and the deplorable status of the tooth #35, before the extraction (Figs. 3A and 3B).

The patient's periodontal treatment included plaque level control and scaling and root planing. A bilateral sinus membrane lifting to increase the bone height or volume from the maxillary sinus floor was implemented; bilateral mandibular ridge augmentation was also performed. After this periodontal treatment period, the plaque level was maintained very low.

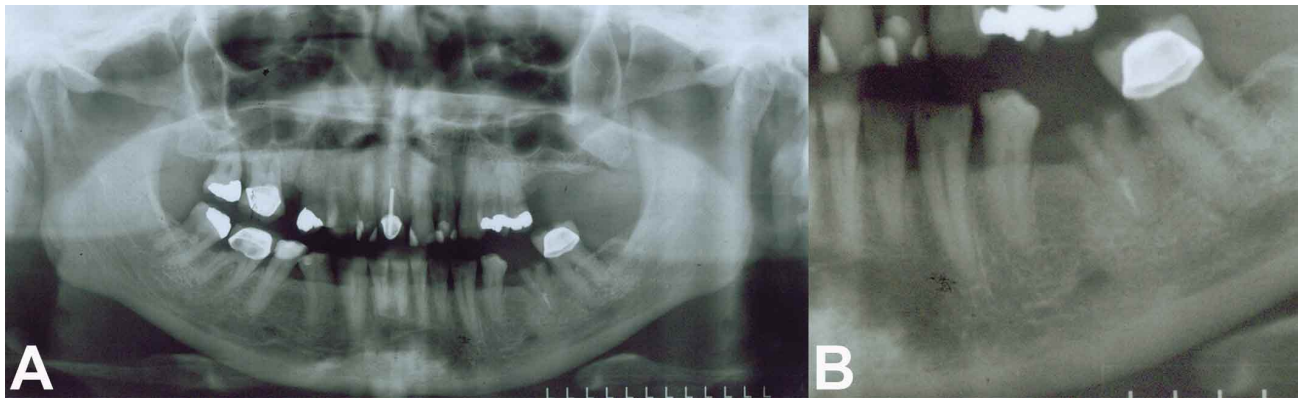


Fig. 3. A and B, radiographs reveal the periodontal condition before the extractions.

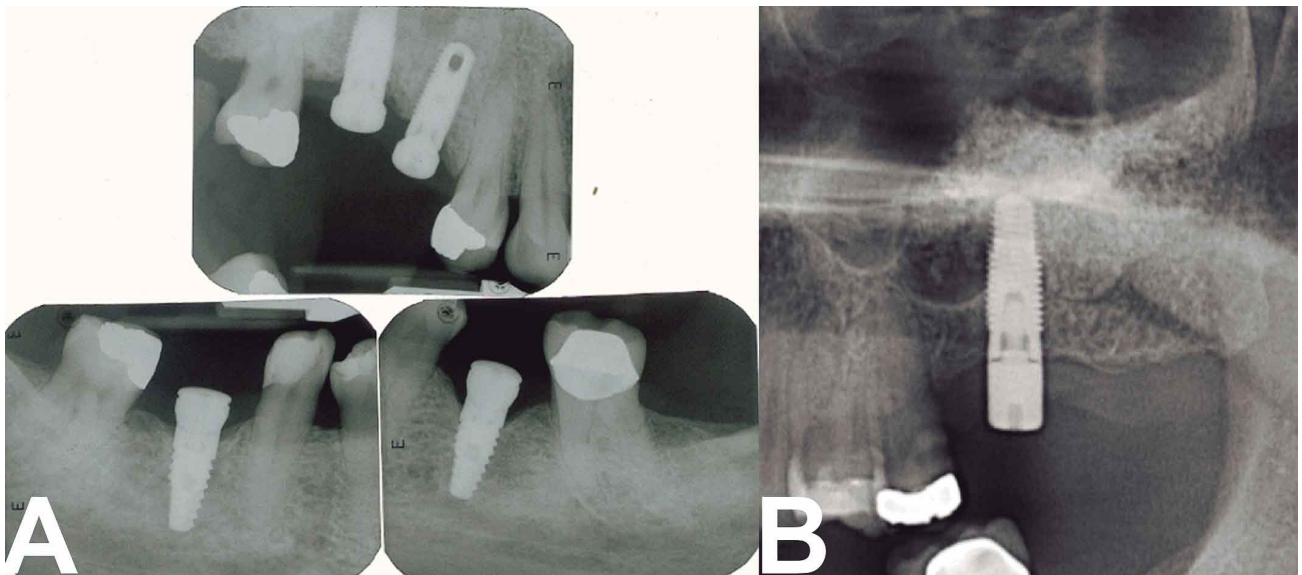


Fig. 4. A and B, implants placed in the maxillary and the mandibular posterior area.

The patient was on a three-month maintenance schedule and on February 2013 five implants (BioHorizons Tapered Internal) were placed in the maxillary (#15, #16, #26) and mandibular (#35, #46) posterior area (Figs. 4A and 4B). The implants were placed at the crestal bone level and were submerged (two-stage approach). These implants had mild horizontal ridge defects at the time of their placement, which was managed with bone graft. Ten days after surgery, the sutures were removed. An interim removable partial denture remained passive over the implant site. Baseline for examination was at the eight weeks' postsurgical evaluation visit. Periapical radiograph showed stable bone around the #35 implant (Fig. 5).

A flapless implant surgery using a soft tissue punch with a circumferential excision of keratinized tissue at the implant site was planned six months after regenerative surgery for the submerged implants. A non-occluding provisional single crown was provided on the #35 implant (Fig. 6). After two months, probing depths up to 12 mm with bleeding on probing and

suppuration were recorded on the #35 implant. The soft tissue surrounding this implant was red and edematous with rolled margins denoting active inflammation. Dental records were obtained for the patient revealing that #35 implant showed radiolucency around and peri-implant bone loss (Figs. 7A and 7B). The diagnosis of early implant failure was made based on criteria defined earlier. The other four implants were clinically healthy and symptom-free (Fig. 7A).

The patient was eligible to undergo a surgical treatment procedure for #35 implant, however previously a microbial culture and in vitro antibiotic resistance testing was done, following standardized protocols (Rams *et al.*). A Gram-negative enteric rod (*Escherichia coli*) was identified. *E. coli* was resistant in vitro to doxycycline, amoxicillin, metronidazole, and clindamycin, but was susceptible in vitro to ciprofloxacin and aminoglycosides (amikacin, gentamicin) in disk diffusion testing. A detailed informed consent was obtained before the surgical treatment. Unfortunately, during the surgical procedure an evident mobility was observed and the implant was removed.

Fig. 5. Periapical radiograph showed stable bone around the #35 implant.

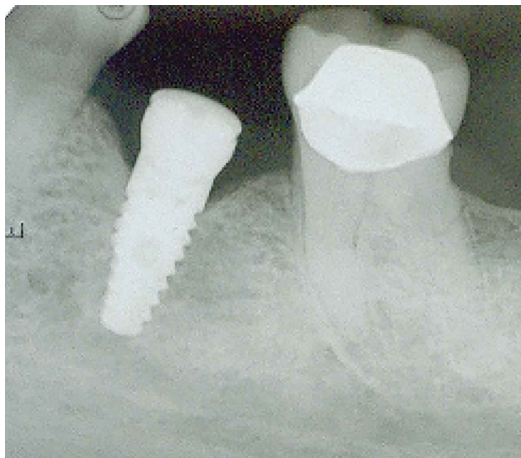


Fig. 6. A non-occluding provisional single crown was provided on the #35 implant.

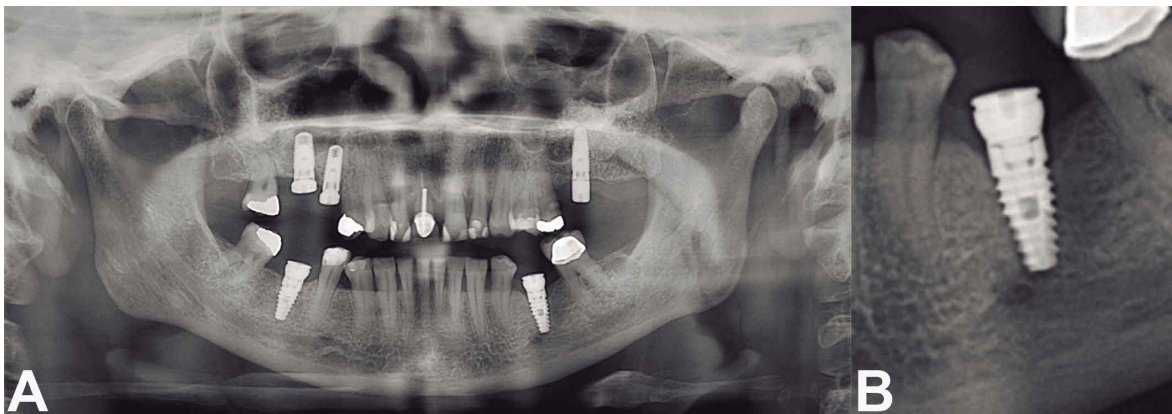
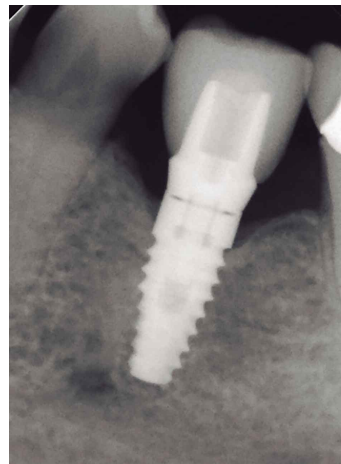


Fig. 7. A and B, #35 implant showing radiolucency around and peri-implant bone loss.

## DISCUSSION

This case presents a possible responsibility of *E. coli* in the pathogenesis of an early implant failure in a partially edentulous patient with a history of localized chronic periodontitis. The microbial conformation of early implant failure and peri-implantitis-associated biofilm is diverse, non-specific and very comparable to that of periodontitis. A substantial exception is the regular occurrence of elevated amounts of staphylococci and enteric bacteria in early implant failure and peri-implantitis (Mombelli *et al.*; Quirynen *et al.*; Belibasakis, 2014). Interestingly, a recent investigation presented that Gram-negative enteric rods in periodontal pockets correlated positively with the presence of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Prevotella intermedia/nigrescens*, also the mean probing depth of the sampled sites was significantly deeper in patients with the presence of Gram-negative enteric rods compared to patients with absence of Gram-negative enteric rods (Ardila *et al.*, 2010).

In order to review the literature related to Pseudomonas/enteric rods-associated to early implant failure and peri-implantitis, a Medline-Pubmed, SCIELO and LILACS search of papers published from 1980 up to and including September 2014, in all languages was conducted, using the following terms in different combinations: "peri-implantitis," "periimplantitis," "periimplant disease," "early implant failure," "implant failure," "Pseudomonas," "Gram-negative enteric rods," "enteric rods" and "enteric." Additional strategies to identify relevant articles included use of Medline's "Related Articles" feature for key articles that were identified from the original search strategy, and bibliographic review of retrieved articles. Only articles involving human studies on individuals were selected for inclusion. Case series, duplicate search results from different combinations of search terms, data unavailable, letters to the editor, historical reviews and unpublished articles were excluded.

Full texts of the selected articles were retrieved. The following data were extracted from all the selected studies: investigators and year of publication of the study, investigation design, age, the number of early implant failure/peri-implantitis patients with enteric rods and sample size of the study, enteric rods identified and its antimicrobial susceptibility. The primary search resulted in 28 publications. By using the exclusion criteria, the reviewers excluded 10 articles as not

relevant to the review, leaving a total of 18 potentially relevant articles that were chosen for retrieval and evaluation of the full text using a data extraction sheet. Out of the 18 full text articles retrieved, 6 articles were excluded because they did not meet the inclusion criteria leaving a total of 12 relevant articles. Table I depicts the list of applicable studies that were retrieved during the data extraction procedure. In order to facilitate the discussion, the results of this case report were included in the same table.

The studies were undertaken between 1987 and 2014, with five studies from the United States (Quirynen *et al.*; Rosenberg *et al.*; Alcoforado *et al.*; Tabanella *et al.*; Listgarten & Lai) three studies from Sweden (Leonhardt *et al.*, 2003; Persson & Renvert) two studies from Colombia (Consuegra *et al.*; Botero *et al.*) one study from Spain (Albertini *et al.*) and one study from Switzerland (Mombelli *et al.*). The sample size of the studies ranged from 9 to 120 patients. The ages of the participants varied between 18 to 90 years. The patients were diagnosed with failing implants (Alcoforado *et al.*; Tabanella *et al.*; Listgarten & Lai; Leonhardt *et al.*, 2003; Mombelli *et al.*), peri-implantitis (Rams *et al.*; Consuegra *et al.*; Botero *et al.*; Albertini *et al.*; Persson & Renvert) bone loss  $\geq 3$  threads (Leonhardt *et al.*, 2003) and infectious failure (Rosenberg *et al.*). The failed implant type incorporated Branemark (Rosenberg *et al.*; Alcoforado *et al.*; Tabanella *et al.*), Nobel Biocare (Leonhardt *et al.*, 2003), 3i (Tabanella *et al.*), ITI (Mombelli *et al.*), core vent (Alcoforado *et al.*; Rams *et al.*), screw vent (Alcoforado *et al.*; Rams *et al.*) and screw type (Botero *et al.*; Albertini *et al.*). All the studies were conducted in partially edentulous patients, except for one implemented in completely edentulous patients (Mombelli *et al.*).

The occurrence of *E. coli* in this report is coherent with earlier culture-based investigations of human early implant failure and peri-implantitis (Rams *et al.*; Belibasakis). Others investigators also observed various species of Pseudomonas and enteric bacteria associated to implant failure (Rosenberg *et al.*; Alcoforado *et al.*). Enteric rods are the principal bacterial family linked to extensive spectrum  $\beta$ -lactamases production of which *E. coli* and *Klebsiella pneumoniae* are most significant. Enteric microorganisms are of clinical prominence producing infections in the central nervous system, lower respiratory tract, bloodstream, gastrointestinal and urinary tract, but are also common



colonizers of the gastrointestinal tract (Brolund, 2014), they can be likewise detected in the subgingival environment of periodontitis individuals (Ardila *et al.*); however, as pointed out by Belibasakis, higher quantities of enteric bacteria have been presented in early implant failure and peri-implantitis compared to periodontitis patients.

Microbes capable of establishing structurally and metabolically ordered cellular aggregates could colonize biomaterials in direct contact with tissues or systemic fluids. Etiological factors of infections associated with biomaterials may include microorganisms comprising the natural microflora of the skin, oral cavity, urinary and reproductive system, the gastrointestinal tract, as well as exogenous organisms. The most commonly isolated bacterial species include enteric bacteria, then, biofilms formed on various medical devices complicate the healing process and become a serious health care issue (Parasion *et al.*, 2014). It seems that titanium dental implants offer an appropriate location for the growth of a multifaceted microbial biofilm. Dental implant design and surface chemistry could likewise have an influence on the incursion of oral microorganisms (Heitz-Mayfield *et al.*). In the present case report a Biohorizons tapered internal implant (4.6 x 10.5 mm) was placed.

Presently, there is no standard protocol for treating early implant failure and peri-implantitis. Several clinical procedures for treating early implant failure and peri-implantitis have been suggested, involving mechanical therapy, adjunctive antiseptics and antibiotics, as well as surgical and regenerative therapy (Rams *et al.*). In the current case a surgical therapy with systemic antimicrobial administration was planned, following the recommendation

Table I. Case report and list of applicable studies that were retrieved during the data extraction procedure.

Authors	Study Design	Age (years) Range	Peri-implantitis patients with opportunistic bacteria/Sample Size*	Microorganisms	Susceptibility
Ardila & Villa-Correa (2015) (Present report)	Case report	54	1/1	<i>Escherichia coli</i>	Ciprofloxacin Aminoglycosides Ciprofloxacin
Albertini <i>et al.</i> (2015)	Cross sectional	32-90	4/33	<i>Pseudomonas aeruginosa</i>	Ceftazidime Aminoglycosides Unreported Unreported
Alcofaredo <i>et al.</i> (1991)	Cross sectional	Unreported	5/18	<i>Pseudomonas aeruginosa</i>	Unreported
Botero <i>et al.</i> (2005)	Cross Sectional	39-58	unreported/11	<i>Enterobacter cloacae</i> <i>Alcaligenes spp</i> <i>Enterobacter agglomerans</i> <i>Pseudomonas aeruginosa</i>	Unreported
Consuegra <i>et al.</i> (2011)	Cross Sectional	42-70	17/55	<i>Klebsiella pneumoniae</i> <i>Escherichia coli</i> <i>Pseudomonas aeruginosa</i>	Unreported
Leonhard <i>et al.</i> (2003)	Prospective Longitudinal	60-77	3/9	<i>Escherichia coli</i> <i>Enterococo cloacae</i>	Ciprofloxacin Sulfonamide/ trimetoprim Unreported
Leonhard <i>et al.</i> (1999)	Cross Sectional	51-79	1 1/37	<i>Klebsiella pneumoniae</i> <i>Escherichia coli</i>	Unreported
Mombelli <i>et al.</i> (1987)	Cross Sectional	Unreported	7/12	<i>unreported</i>	Unreported
Listgarten & Lai (1999)	Cross Sectional	57-61	4/41	<i>unreported</i>	Unreported
Persson & Renvert (2013)	Cross Sectional	18-88	1/66	<i>Pseudomonas aeruginosa</i>	Unreported
Rams <i>et al.</i> (2014)	Cross Sectional	28-90	7/120	<i>Escherichia coli</i>	Ciprofloxacin
Rosenberg <i>et al.</i> (1991)	Cross Sectional	Unreported	6/11	<i>Pseudomonas aeruginosa</i> <i>Klebsiella pneumoniae</i>	Unreported
Tabanella <i>et al.</i> (2009)	Cross sectional	31-72	2-15	<i>unreported</i>	Unreported

\*Number of patients

of a very recent systematic review (Mombelli *et al.*). The purpose of this procedure is to disturb the integrity of the biofilm and detach the vast majority of the microorganisms. Besides, a flap surgery is recommended in case of pus formation (Leonhardt *et al.*)

*Pseudomonas aeruginosa* and *E. coli* were the most frequent of the opportunistic bacteria found in this review (six and five studies respectively), results consistent with this report. *P. aeruginosa* has likely been the first pathogen to exhibit multidrug-resistance and extremely drug-resistance phenotypes, with the emergence of strains resistant to all classes of anti-pseudomonal agents except polymyxins. On the other hand, *E. coli* is also multidrug-resistance producing extended-spectrum beta-lactamases, then surveillance, infection control practices and optimization of the available antimicrobial therapy regimens are needed (Ardila *et al.*).

In the present report, *E. coli* was resistant in vitro to doxycycline, amoxicillin, metronidazole, and clindamycin, but was sensible in vitro to ciprofloxacin and aminoglycosides which exerts only weak efficacy against periodontal anaerobic bacteria. Thus, the use of ciprofloxacin plus metronidazole, for adjunctive antibiotic treatment must be considered (Ardila *et al.*). Similar in vitro results have been documented in three publications included in this revision (Rams *et al.*; Leonhardt *et al.*, 1999; Albertini *et al.*). The only prospective study included in the present revision (Leonhardt *et al.*, 2003), showed that three patients had enteric rods at baseline while none were colonized with enteric rods after five years. All were treated with surgical therapy plus antibiotics. A female smoker with two implants, both harboring *E. coli* was treated; following surgical treatment, therapy with ciprofloxacin for two weeks was prescribed and the *E. coli* was not further detected during the five year follow-up period. However, one implant was lost before the end of the study.

This elucidates the changeability of antibiotic sensitive forms that may appear in diverse facultative-anaerobic bacterial pathogen populations on failing dental implants, and the latent difficulties confronted by clinicians considering selection and management of peri-implantitis antimicrobial therapies (Rams *et al.*). Interestingly, Ardila *et al.* found high levels of opportunistic bacteria (including *P. aeruginosa* and *Klebsiella pneumoniae*) in patients with chronic periodontitis and in their investigation moxifloxacin

appeared capable of eradicating these organisms from periodontal pockets. Moxifloxacin showed good activity against Gram-negative enteric rods, *Pseudomonas* and periodontopathogens suggesting the potential use of moxifloxacin as an adjunctive antibiotic in the treatment of mixed periodontal infections. Rams *et al.* suggested that microbiological analysis and in vitro antibiotic susceptibility testing of cultivable isolates may support in the selection of proper antimicrobial therapy regimens for peri-implantitis, similar recommendation was mentioned in early implant failure (Tabanella *et al.*).

Although in the current case report the presence of *E. coli* was observed in a failed implant, this does not essentially demonstrate a causal relationship. However, several investigations demonstrated an association between the presence of Gram-negative enteric rods and *Pseudomonas* with failed implants. An antibiotic sensitive testing of cultivable subgingival microorganisms including periodontal pathogens and opportunistic bacteria are recommended in patients with early implant failed and peri-implantitis, considering their mixed infections and ample disparity in observing drug resistance patterns.

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**ARDILA, M. C. M. & VILLA-CORREA, Y. A.** Bacilos entéricos gram-negativos asociados a fracaso temprano de implantes y peri-implantitis: Reporte de un caso y revisión sistemática de literatura. *Int. J. Odontostomat.*, 9(2):329-336, 2015.

**RESUMEN:** La microbiota asociada con los implantes fallidos incluye *Pseudomonas* y bacilos entéricos Gram-negativos. En el presente estudio se informa acerca de un caso de *Escherichia coli* asociada a un fallo temprano del implante resistente in vitro a la doxiciclina, amoxicilina, metronidazol y clindamicina, pero susceptible in vitro a ciprofloxacina y aminoglucósidos. Se realizó una revisión de la literatura sobre la prevalencia de los microorganismos oportunistas en pacientes con insuficiencia temprana del implante y periimplantitis, y el tratamiento habitual de estos pacientes portadores de *Pseudomonas* y bacilos entéricos.

**PALABRAS CLAVE:** peri-implantitis, bacilos entéricos, *Pseudomonas*, fracaso de implante.

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