Effect of Adjunct Antibiotics in the Treatment of Peri-Implant Disease: A Systematic Review and Meta-Analysis

Ya-Wei Chen
dryawei@alumni.upenn.edu

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Abstract

Aim: The aim of this systematic review was to assess the clinical effect of adjunct antibiotics in the treatment of peri-implant diseases. Materials and Methods: An electronic systematic search was conducted by using the following databases: PubMed (Medline), Elsevier EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), EBSCO-Dentistry and Oral Science Source, and WHO International Clinical Trials Registry Platform (WHOINT) from January 1980 to March 2020 (Registration in PROSPERO:CRD42018114147). Randomized controlled clinical trials with at least 10 patients with peri-implant diseases, treated with or without adjunct local or systemic antibiotics along with surgical or non-surgical therapies, and minimal three months follow up were included. Meta-analyses were performed to analyze weighted mean differences (WMD) in pocket depth (PD) reduction, radiographic bone level (RBL) gain, and odds ratio (OR) of treatment success. Subgroup analyses were conducted based on different diseases or type of antibiotics. Results: From 856 articles identified, 10 articles met the inclusion criteria were selected. Among them, 6 articles were included for meta-analysis. Adjunct antibiotics in the treatment of peri-implant diseases showed significant more PD reduction (3 mo: WMD = 0.56 mm, \( p = 0.001 \); 6 mo: WMD = 0.77 mm, \( p < 0.00001 \); 12 mo: WMD = 0.92 mm, \( p < 0.00001 \)), RBL gain (WMD = 0.64 mm, \( p = 0.03 \)) and treatment success (OR = 1.74, \( p = 0.04 \)) compared to the same treatment without adjunct antibiotics. Subgroup analysis showed the clinical benefit of antibiotics is especially significant in the treatment of peri-implantitis, not as much in peri-implant mucositis. Conclusion: From the current evidence, adjunct antibiotics provided additional beneficial effect up to 12 months in the treatment of peri-implant diseases, including PD reduction, RBL gain and treatment success.
Effect of Adjunct Antibiotics in the Treatment of Peri-Implant Disease: A Systematic Review and Meta-Analysis

Ya-Wei Chen, DDS
University of Pennsylvania
yawec@upenn.edu

Thesis

Presented to the Faculty of Penn Dental Medicine in Fulfillment of the Requirements for the Degree of Master of Science in Oral Biology

Thesis Committee:

Dr. Jonathan Korostoff DMD, PhD

Dr. Joseph Fiorellini DDS, DMSc

Dr. Yu Wang DDS, DMD, MDS, MS

Dr. Campo Perez, DDS, MS
# Table of Contents

Abstract .................................................................................................................. 3

Acknowledgements ............................................................................................... 4

Review of pertinent literature ............................................................................. 5

Objectives ............................................................................................................... 15

Statement of the PICO question ......................................................................... 16

Introduction ........................................................................................................... 17

Material and methods ......................................................................................... 19

Results ................................................................................................................... 24

Discussion ............................................................................................................. 40

Conclusion ............................................................................................................ 44

References ............................................................................................................ 45
Abstract

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Acknowledgement

First and foremost, I would like to thank Dr. Jonathan Korostoff, clinical director of the Department of Periodontics and director of the Master of Science in Oral Biology program, and Dr. Joseph Fiorellini, director of the Department of Periodontics, for granting me the opportunity to pursue this coursework. I would also like to thank Dr. Yu Wang, for providing valuable periodontal and microbiological insights into this project.

Last but not least, I would like to thank my family for being beside me and support me. I couldn’t have done this without you all.
Review of Pertinent Literature

History of Modern Implant Dentistry and Concept of Osseointegration

The era of modern implant dentistry was stemmed in 1952, when the Swedish orthopedic surgeon Per-Ingvar Brånemark inadvertently discovered osseointegration between an implant and the rabbit bone using vital microscopy. Recognizing the value of osseointegration, Dr. Bränemark and his colleagues, as well as other Europeans (including Switzerland’s Andre Schroeder at the University of Berne), started to research the clinical application of osseointegration in dentistry.1 By 1978, the National Institutes of Health-Harvard University consensus conference was held to examine the model development, benefits, and risks of dental implants, as well as a successful dental implantation procedure for clinicians to follow.2 This conference marked the transition out of an era in which implants were considered as an unreliable and just an experimental method for tooth replacement.

To fulfill the procedural guide for dental implantation, Albrektsson et al conducted a human study in 1981 and gave one of the first definitions of dental implant osseointegration. They examined thirty-eight long-term functioning threaded, cylindrical titanium implants from jawbones, tibial bones, or iliac bones for histological ultrastructural analysis. Using the X-rays, stereomicroscope and transmission electron microscope, they were able to take a closer look at the bone-implant interface. They found that no wear products were seen in the bone or soft tissues in spite of 90 months of loading times. The bone covering the implants appeared as dense lamellae, and the collagen fibers were tightly adhered to titanium surface; while the soft tissues on the upper part of jawbone implants were closely adhere to titanium surface to form a biological seal. The cells on that soft tissue-implant inter-surface were polygonal epithelial cells, but no white blood cells nor any types of inflammatory cells infiltrating the border area. The author then described
osseointegration as a “direct functional and structural connection between living bone and the surface of a load-bearing implant”.

Subsequently, Branemark also illustrated the concept of osseointegration in a more detailed manner. He described that the interface between tissue and the integrated titanium tooth root implants was “a shell of compact cortical bone formed around the implant without any apparent soft tissue intervention between normal bone and the surface of the implant”. Therefore, osseointegration unites bone to an implant surface, with a direct structural and functional connection without intermediate fibrous tissue or fibrocartilage formation.

Besides the histological point of view, clinical studies since 1978 at the Harvard Conference have proven the predictability of biological healing of dental implants and mechanical function of implant prosthesis. In 1981, a longitudinal study of 2768 implants (371 consecutive patients) with fixed implant prostheses on edentulous jawbones was conducted by Adell et al, which showed that 81% of maxillary implants and 91% of mandibular implants remained stable after an observation time of 5-9 years. The article also revealed that the mean bone loss was 1.5mm on the upper jaw and 0.7mm on the lower jaw during the healing period (from fixture installation to abutment connection). After abutment connection, only 0.1mm of marginal bone was lost annually during the remodeling period.

**Implant Success and Failure**

Many experimental and clinical studies have been conducted after then, to focus on the mechanism of tissue integration in different types and designs of the implants, reasons of implant failure, and how to secure long-term success. In the beginning, the definitions on implant success or failure were very arbitrary and based on anecdotal clinical observations. Implant was considered successful when it meets its defined success criteria in terms of function (ability to chew), tissue
physiology (presence of osseointegration, absence of pain and other pathological processes), and user satisfaction (esthetics and absence of discomfort). In 1986, Albrektsson proposed a minimum criteria for the dental implant success, which included (1) an individual, unattached implant is immobile, (2) radiographically no evidence of peri-implant radiolucency, (3) vertical bone loss less than 0.2mm annually following the implant’s first year of service, (4) absence of persistent and/ or irreversible signs and symptoms such as pain, infections, neuropathies, paresthesia, or violation of the mandibular canal, (5) in the context of the above, they reported a successful rate of 85% at the end of a five-year observation period and 80% at the ten-year period. This criteria was widely used for defining implant success in clinical studies and practice, however, it did not address the process of tissue changes around implants, which led to the loss of implants.

While implant failure is the term used for implants that require removal or have already been lost, failing implant is the term to be used where any symptoms or signs are distinguished as early changes preceding the loss of osseointegration. In 2008, a group of clinicians in the International Congress of Oral Implantologists (ICOI) published a consensus article in the journal Implant Dentistry with the updated definition on implant success, implant survival, and implant failure. From their definition of implant success, it is suggested to include a time period of at least one year for implants serving as prosthetic abutments. And there are three life spans determining the early, intermediate, and long-term success of implants: Early success spans 1 to 3 years, intermediate success spans 3 to 7 years, and long-term success spans more than 7 years. They also provided the scales and criteria of implant quality of health for the clinicians to evaluate and then to treat the condition accordingly (see Table 1).

Table 1. ICOI Implant Quality Scale
<table>
<thead>
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<th>Implant Quality Scale</th>
<th>Clinical conditions</th>
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| Success                     | • No pain or tenderness upon function  
• No mobility  
• <2mm radiographic bone loss from initial surgery  
• No exudates history                                                                                       |
| Satisfactory survival       | • No pain on function  
• No mobility  
• 2-4mm radiographic bone loss from initial surgery  
• No exudates history                                                                                       |
| Compromised survival        | • May have sensitivity on function  
• No mobility  
• >4mm radiographic bone loss from initial surgery (less than ½ of implant body)  
• Probing depth >7mm  
• May have exudates history                                                                                      |
| Failure                     | Any of the following  
• Pain on function  
• Mobility  
• Radiographic bone loss > ½ length of implant  
• Uncontrolled exudate  
• No longer in mouth                                                                                       |

**Failing Implant**

To prevent implant failure, the utmost is to understand the factors related to implant loss and the process of implant failing. Implant failures can be resulted from (1) biological complications, (2) mechanical or technical complications, (3) inadequate patient adaptation. Mechanical or technical complications serve as a collective term for mechanical damage of the implant, implant components, or supra-structures. They should and could be avoided by adequate design of implants by the manufacturers, as well as adequate treatment planning and treatment administration by the clinicians. Inadequate patient adaptation is related to psychological, esthetical, and phonetical problems. Biological complications refer to disturbances in the function of implants characterized by biological processes that affect the tissues supporting the implants. Biological complications can further be subdivided into early and late complications: Early
complications happen before the implant loading, while late complications happen after implant loading.\textsuperscript{12}

Radiographic evidence of bone loss around the implants provides essential information for the assessment of implant outcome. So far, no reference in the literature can indicate the amount or rate of bone loss which ultimate leads to implant failures. Peri-implant bone loss may be resulted from normal remodeling to overloading, microgap leakage, or inflammation/ infection.\textsuperscript{13} Albrektsson and Isidor defined an inflammatory process which affect the soft and hard tissues surrounding osseointegrated dental implants as peri-implant diseases.\textsuperscript{14} Peri-implant disease include peri-implant mucositis and peri-implantitis. Peri-implant mucositis is reversible inflammatory reaction confined to soft tissues around the implants, while peri-implantitis refers to inflammatory condition extends to the supporting bone.\textsuperscript{15} Previous studies have shown the prevalence rate of peri-implant mucositis is approximately 80\% of the subjects and in 50\% of the implants,\textsuperscript{16} while peri-implantitis was found in between 28\% and 56\% of subjects and 12 to 43\% of implants over 5 years of follow-up.\textsuperscript{15,17}

\textbf{Etiology and Pathophysiology of Peri-Implant Diseases}

According to the definition, any sign of bone loss from inflammation may be interpreted as indicative of peri-implantitis. Evidence has shown that poor oral hygiene, smoking, history of periodontitis, diabetes, genetic traits, alcohol consumption and some implant surface are potential risk indicators for peri-implant disease.\textsuperscript{18} As a local factor, a well-functioning marginal mucoperiosteal-osseous barrier zone is a key to maintain a healthy state around a dental implant. To elucidate the marginal tissue reactions after implant insertion, several studies have been conducted based on animal models or human trials.
In 1986, a cross-sectional study was conducted by Lekholm. He had participants selected randomly from a pool of 400 subjects. All the patients had implants and fixed dentures for at least 6 months to 15 years. Samples of subgingival microbiota were harvested by curettes from the sites showing the deepest and shallowest pockets in each jaw of patient. In this study, only 45% of the abutments were free of plaque, and 80% of abutments were surrounded by inflammatory gingiva. The presence of plaque and gingivitis was significantly correlated. And significant correlations were established between presence of gingivitis or deeper pockets and occurrence of filiforms and small spirochetes. This study illustrated that microbial plaque could be associated with the ecosystem around dental implants and plays a role in inflammation of gingiva around the implants.

Then in 1987, Mombelli conducted a study to compare the composition of the microbiota around “successful” and “failing” implants. The author selected patients from a recall group of implant wearers who had 2 or 4 hollow cylinder titanium implants on the mandible for more than 1 year. Based on a threshold of 5mm probing depth, the patients were divided into either successful group (Group S) or failing group (Group U). The clinical parameters retrieved were plaque index, sulcus bleeding index, and gingival index. For darkfield microscopic examination of microbiota, subgingival samples were obtained from 2 sites of contralateral implants in Group S, while the healthiest and most diseased site were chosen in Group U. Their results showed that in group S, the predominant morphotype of bacteria were coccoid, and no spirochetes were found. However, significantly elevated count of anaerobic bacteria was found in the diseased site of group U. Gram-negative anaerobic rods accounted for more than 50% of cell count in more than one half of the samples. Black pigmented Bacteroides, especially Bacteroides intermedius, were found regularly and accounted for up to 30% of the total cultivated microbiota. Fusobacterium spp. were also commonly found around failing implants, comprising mean proportions of 15.3% of anaerobic
count. They concluded that the composition of subgingival plaque samples varied considerably when taken from healthy or diseased implant sites within the same patients, and peri-implantitis should be regarded as a site-specific infection.\(^{20}\)

In 1992, Berglundh and Lindhe et al performed an experiment on animal models to examine the soft tissue reaction to de novo plaque formation on implants and to compare with the reaction around teeth. They found a similar barrier function tissue reaction on the gingiva around implants to teeth. They both had increase of the leukocyte transmigration in the junctional epithelium, and the volume occupied by inflammatory cells in the two connective tissue lesions was also similar.\(^{21}\) In 1994, Pontoriero et al conducted an experimental human study to compare the clinical and microbiological parameters during the development of gingivitis and peri-implant mucositis 6 months following implant installation. The results showed that after 3-week period of no oral hygiene care, the clinical index values increased significantly at both implant and tooth sites. Plaque accumulation was at similar rates and the mean values of clinical parameters were also very similar at implant site and tooth site at any observation periods.\(^{22}\)

In 2000, Van Winkelhoff et al studied the early colonization of peri-implant pockets by putative periodontal pathogens in 20 partially edentulous patients. The authors found the most commonly seen periodontal pathogens, *P. gingivalis, F. nucleatum, P. intermedia, and T. forsythia*, were identified as early as 6 months after loading. In particular, *P. gingivalis* was significantly associated with the presence of fistula and implant loss.\(^{23}\)

Lastly, a recent review article which collected 29 reports on subjects with peri-implant diseases revealed that in most cases the composition of the flora is similar to the subgingival flora of chronic periodontitis and is dominated by Gram-negative bacteria. They concluded peri-implant diseases can be viewed as a mixed anaerobic infection.\(^{24}\) From all these evidence, it is well
demonstrated that the combination of multiple pathogenic bacteria in the subgingival plaque plays an important role in the initiation and progression of peri-implant diseases. And the reduction of the bacterial load to a level compatible with health is an important aspect in the treatment of peri-implant diseases.\textsuperscript{25}

**Diagnosis of Peri-implant Diseases**

The consensus report on the definition, diagnosis, and treatment of peri-implant diseases was once published in 2008 at the 6\textsuperscript{th} European workshop on periodontology. By that time the clinical diagnosis of peri-implant disease was still very vague. For example, they stated that probing is essential for diagnosis of peri-implant diseases, and bleeding on probing indicates the presence of inflammation in the peri-implant mucosa. They also mentioned an increase in probing depth over time is associated with the loss of attachment and supporting bone.\textsuperscript{17} No definitive cut off value for probing depth or bone loss was provided. Later, the American Academy of Periodontology also published a statement on peri-implant mucositis and peri-implantitis in regard to the diagnosis and clinical implications in 2013. In this report, they suggested that the signs to determine peri-implant mucositis include bleeding on probing and/or suppuration, with associated probing depths $\geq 4$mm and no evidence of radiographic bone loss beyond bone remodeling. However, when these parameters are present with any degree of detectable bone loss following the initial bone remodeling after implant placement, a diagnosis of peri-implantitis is made. If no baseline radiograph is available, then a threshold vertical distance of 2mm from the expected marginal bone level following remodeling should be used for diagnosing peri-implantitis.\textsuperscript{26}

The most recent classification for peri-implant diseases and conditions was presented by the Workgroup 4 of the 2017 world workshop. Five position articles described the characteristics
of peri-implant mucositis, peri-implantitis, and soft/ hard tissue deficiencies. To diagnose peri-implant mucositis, it requires (1) presence of bleeding and/ or suppuration on probing with or without increased probing depth compared to previous examinations, and (2) absence of bone loss beyond crestal bone level changes resulting from initial bone remodeling. To diagnose peri-implantitis, it requires (1) presence of bleeding and/ or suppuration on probing, (2) increased probing depth compared to previous examinations, and (3) presence of bone loss beyond crestal bone level changes resulting from initial bone remodeling. If in the absence of previous examination data, then the diagnosis of peri-implantitis can be based on the combination of (1) presence of bleeding and/ or suppuration on gentle probing, (2) probing depths of $\geq 6$mm, and (3) bone levels $\geq 3$mm apical of the most coronal portion of the intraosseous part of the implant.  

**Management of Peri-implant Disease**

Based on the notion that the development of subgingival microflora is associated with peri-implant diseases, decrease bacterial load from the implant surface becomes the main objective in the treatment of peri-implant mucositis and peri-implantitis.  

Peri-implant mucositis is believed to be the precursor of peri-implantitis, in the same way that gingivitis is the precursor of periodontitis. Mechanical therapy with or without adjunctive use of antiseptic rinses is usually the initial treatment of choice. Patient’s plaque control is also an important factor for treatment success.  

In regard to peri-implantitis, various non-surgical and surgical therapies have been advocated to eliminate the established biofilm and to resolve peri-implant infection and restore peri-implant tissues. These therapies include mechanical debridement of the implant surface, chemical conditioning of the implant surface, laser therapy, implantoplasty, access flap surgery
with or without regenerative procedures, as well as topical or systemic antibiotics and/ or antimicrobial therapy.\textsuperscript{29, 30}

In 2012, a systematic review of randomized clinical trials was conducted with the aim to evaluate the efficacy of non-surgical treatment of peri-implantitis. It showed that submucosal debridement with adjunctive local antibiotics, glycine powder air polishing, or Er:YAG laser treatment may reduce clinical signs of peri-implant mucosal inflammation relative to submucosal debridement with adjunctive irrigation with chlorhexidine. However, there was still lack of result on the efficacy of non-surgical therapy on bone loss or implant survival rates in this study.\textsuperscript{31}

Another systematic review in 2013 looked at the effectiveness of reconstructive procedures for treating peri-implantitis. Only 1 randomized controlled trial was found at that time, thus case series studies were also included in that systematic review, with a total of 12 studies finally included. The results showed that reconstructive therapies with the combination of implant surface detoxification, different grafting material and membranes had a weighted mean radiographic defect fill of 2.17mm (95% confidence internal (CI): 1.46-2.87mm), a probing depth reduction of 2.97mm (95% CI 2.38- 3.56mm), clinical attachment level gain of 1.65mm (95% CI: 1.17-2.13mm), and bleeding on probing reduction of 45.8% (95% CI 38.5-53.3%) for $\geq$ 12 months of follow-up.\textsuperscript{32}

To date, there is still no consensus on the best treatment modality for peri-implantitis. But to cocktail different treatment methods to reduce pathogenic bacteria to greater extent should still be the utmost consideration in order to save failing implants due to peri-implantitis.

**Objectives**
Since biofilm is a recognizable etiological factor for peri-implant diseases, it is hypothesized that local or systemic delivery of antibiotics combined with the mechanical debridement may eliminate pathogenic bacteria to a greater extent compared to the mechanical treatment. The evidence on the adjunct use of antibiotics on peri-implant diseases, however, remains insufficient\textsuperscript{33, 34}. Therefore, the aim of the current systematic review and meta-analyses is to assess the clinical and microbiological effects of adjunct use of local or systemic antibiotics in the treatment of peri-implant diseases.
Statement of PICO Question

**PICO question** - *Does adjunct antibiotics have additional clinical or microbiological effect on the treatment of peri-implant diseases compared to treatment without adjunct antibiotics?*

**P:** patients with peri-implant diseases

**I:** surgical or non-surgical treatment for peri-implant diseases adding adjunct antibiotics

**C:** surgical or non-surgical treatment for peri-implant disease without adding adjunct antibiotics

**O:** outcome measures regarding clinical parameters, treatment success, and microbiological shift
Introduction

Dental implants have become a reliable alternative treatment for missing tooth in day-to-day practice. With an increasing number of implant placements, the prevalence of peri-implant diseases has also increased over time\textsuperscript{35, 36}. At the First European Workshop on Periodontology in 1993, peri-implant diseases were defined as destructive inflammatory processes affecting the soft and hard tissues surrounding osseointegrated dental implants in function\textsuperscript{14}. There are two types of peri-implant diseases; peri-implant mucositis: a reversible inflammatory reaction confined to soft tissues and peri-implantitis which irreversibly extends to the supporting bone\textsuperscript{14, 15}.

Extensive evidence has shown that bacteria in the subgingival plaque plays an important role in the initiation and progression of peri-implant diseases\textsuperscript{37-41}. Hence, the goal of peri-implant diseases treatment is to decrease the total bacterial load. Various non-surgical and surgical therapies have been advocated to approach this goal with conflicting outcomes having been reported, these therapies include: mechanical surface debridement, laser treatment, implantoplasty, resective and regenerative surgical procedures\textsuperscript{29, 42-45}. Since outcomes of peri-implant disease therapies are unpredictable, it has been suggested that anti-infective measures should also be included into the treatment\textsuperscript{17, 43, 46, 47}.

Based on the understanding that biofilm is relatively resistant to antimicrobial therapy, administration of antibiotics accompanied by disruption of plaque with mechanical debridement is a widely accepted treatment modality\textsuperscript{24, 48, 49}. Consequently, the adjunct use of antibiotics has been extensively studied and has consistently shown to provide clinical benefits in the treatment
of periodontitis\textsuperscript{50, 51}. With the hypothesis that peri-implant pathogens might be easily retained on the rough implant surfaces capable of invading soft tissue, this supportive treatment has also been applied to peri-implant diseases\textsuperscript{52}. However, the benefit of adjunct use of antibiotics for peri-implant diseases remains controversial\textsuperscript{33, 43, 53}.

The previous reviews discussing antibiotics in the treatment of peri-implant diseases highlighted the need of more randomized controlled trials (RCTs) to strengthen the evidence\textsuperscript{33, 43}. To our knowledge, no meta-analysis has been conducted to evaluate the additional use of antibiotics in surgical or non-surgical peri-implant treatment. Therefore, the aim of this systematic review and meta-analysis of RCTs was to assess the clinical and microbiological effects of adjunct use of localized or systemic antibiotics in the treatment of peri-implant diseases.
Material and Methods

This article adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines\textsuperscript{54} for developing a focused question in PICO (participants, interventions, comparison, outcomes) format, which is: “Does adjunct antibiotics (I) have any favorable effect upon clinical parameters or microbiological shift (O) in patients with peri-implant diseases (P), compared to any treatment without adjunct antibiotics?” A protocol was registered at PROSPERO (Registration No. CRD42018114147) before this systematic review and meta-analysis was started to avoid potential biases.

Search strategy

A systematic search was conducted by a librarian (L.G.) to address the PICO question through the following databases: PubMed (Medline), Elsevier EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL), EBSCO-Dentistry and Oral Science Source, and WHO International Clinical Trials Registry Platform (WHOINT). Articles from 1980 forward until March 25, 2020 were searched. The search terms included medical subject headings (MeSH/EMTREE) and free text/keywords by different combinations, and the strategy was as followed: $$(((\text{"Anti-Infective Agents"}[Mesh] \ OR \ "\text{Anti-Bacterial Agents"}[Mesh] \ OR \ "\text{Anti-Bacterial Agents"}[\text{Pharmacological Action}]) \ OR \ \text{anti-biotic}^* \ OR \ \text{antibiotic}^* \ OR \ "\text{anti biotic}" \ OR \ \text{anti-bacterial} \ OR \ \text{antibacterial}))) \ AND \ (((\text{"\text{Peri-Implantitis"}[Mesh] \ OR \ \text{peri implantitis} \ OR \ \text{peri-implantitis} \ OR \ "\text{peri implantitis}" \ OR \ \text{peri-implant}^* \ OR \ "\text{peri implant}" \ OR \ \text{periimplant}^*))) \ OR \ (((\text{"\text{Periodontal Diseases"}[Mesh] \ OR \ \text{periodontal} \ OR \ \text{periodontitis} \ OR \ \text{bony defect} \ OR \ "\text{bone loss}")))$$
OR ("Inflammation"[Mesh])) AND ("Dental Implants"[Mesh] OR tooth implant OR teeth implant))).)

Two reviewers (Y-W.C., Y.W.) conducted title, abstract, and full text screenings independently after pre-screening calibration and standardization in selection criteria were performed. If the study passed title and abstract screen, the full-text of the article was reviewed. When the abstract of the articles were not available, the full-text studies were reviewed. Any disagreement between the two reviewers was discussed and resolved by consultation with the third author (C-Y. C.).

Authors of the included studies were contacted to clarify any questions or issues of missing data when necessary. When there was more than one publication reporting on the same patient groups, all the studies were reviewed and the data was examined based on the determined selection criteria.

**Study selection criteria**

Studies were included when they met the following inclusion criteria: patients included in study had peri-implant mucositis or peri-implantitis treated with any treatment with a combination of adjunct antibiotics (ABX group), either systemic or local-delivered; the comparator was the same treatment without adjunct antibiotics (control group); primary outcomes included were probing depth (PD) reduction, radiographic bone level (RBL) gain, and treatment success. The secondary outcomes were bleeding on probing (BOP) and microbiological shift before and after the treatments.
Additionally, studies had to meet the following criteria: (1) RCTs with at least 10 subjects enrolled in each group, (2) follow-up period of at least three months after treatment, (3) published in English, Chinese, or Greek. Exclusion criteria: Studies lacking a control group were excluded.

**Qualify assessment of studies**

The risk of bias (RoB) assessment of the studies was evaluated using the revised Cochrane risk-of-bias tool for randomized trial (Cochrane RoB 2.0)\(^5^5\). The following five domains were assessed: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. After evaluating each domain, the overall RoB assessment of each study was ranked as followed, “Low” RoB if all domains were low RoB; “Some concerns” when if at least one domain was judged to have some concern ; and “High” RoB when at least one domain had high RoB or multiple domains were judged to have some concerns that substantially lowered the confidence in results.

Two authors (Y-W.C., Y.W.) independently performed the assessment. Any discrepancy was resolved between the two authors to reach an agreement.

**Data extraction**

A standardized tabulation was generated by one author (Y-W.C.) to facilitate data extraction, in which the following items were included: study design, patient demographics, types of peri-implant diseases, primary treatment modalities, types of adjunct antibiotics, antibiotics delivery method, and follow up period. Variables regarding outcome measurements were independently retrieved by two reviewers (Y-W.C., Y.W.), which included: (1) sample size of patients and number of implants with peri-implant diseases, (2) changes on BOP, (3) changes on
PD, (4) changes on RBL, (5) number of treatment success, and (6) microbiological examination findings. The data for each study were entered into electronic spreadsheets.

**Data synthesis and analysis**

We calculated PD reduction by subtracting the PD at the follow-up measurement from the PD before treatments were given. The weighted mean difference of PD reduction (WMDPD) were estimated by subtracting the PD reduction in the ABX group from PD reduction in the control group. A positive value indicated that the ABX group had more PD reduction than the control group and vice versa. Then we pooled the differences of PD reduction between two groups in each study on the basis of assigned weights. For the changes in radiographic bone level (RBL). We calculated RBL gain by subtracting the bone level at the last measurement from the bone level at baseline. We calculated the weighted mean difference of RBL gain (WMDRBG) by subtracting the RBL gain in the ABX group from the RBL gain in the control group. Then we pooled the differences of RBL gain between two groups in each study on the basis of the assigned weights. A positive value of WMDRBG indicated that ABX group had more bone gain than the control group and vice versa. Odds ratio (OR) for ABX group and control group were used to calculate overall treatment success rate, presented by weighted pooled odds ratio (WPOR). We also looked at BOP and microbiological findings, which were synthesized without meta-analysis.

Random effects meta-analyses of the selected studies were applied to avoid any bias caused by methodological differences among the studies. Forest plots were generated to graphically represent the difference in outcomes of ABX and control groups for all included studies, using the implant as the unit of analysis. If the study included multiple groups that qualified for data analysis, we extracted the data from each group and treated each data set independently. For the paired data
obtained from the pre-post studies, the correlation was calculated and used for meta-analysis. An estimated correlation value would be assumed for studies that did not report enough information to calculate the correlation (standard deviations of the baseline, post-intervention and difference). Heterogeneity was assessed using $I^2$ tests, which ranged between 0% and 100%; lower values represented less heterogeneity. To evaluate the variables causing heterogeneity or result bias, we conducted subgroup analysis. All statistical analysis was performed (by C-Y. C.) using the Review Manager (RevMan) software (Review Manager, version 5.3, The Nordic Cochrane Center, Copenhagen, Denmark). A $P$ value of .05 was used as the level of significance.

**Grading of evidence**

According to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, the quality of evidence was assigned to each outcome across studies by the following criteria: Study design, risk of bias, consistency, precision, publication bias and, other considerations. Consistency was judged based on the heterogeneity ($I^2$) of each outcome, and was ranked as: Not serious, 0-30%; serious, 30-75%; and very serious, > 75%. Precision was judged based on total sample size; it was ranked as not serious if total sample size was larger than 40, serious if between 20-40, and very serious if smaller than 20. Publication bias was assessed when outcomes had more than 10 articles included for quantitative analysis. The GRADE system results in four grades in rating the quality of evidence: high, moderate, low and very low.
Results

A total of 856 non-duplicated articles were found by the search strategy (Figure 1). We identified 54 articles after reviewing the titles and abstracts. After full text review, 44 articles were excluded due to wrong study design, wrong treatment, or incomplete data for outcome assessments. Finally, 10 articles met the inclusion criteria and qualified for qualitative assessment and descriptive synthesis. Among those studies, a study done by Carcuac in 2017 used the same cohort as the 2016 study done by the same author but with different follow-up periods. Three studies were not used for meta-analysis due to lack of available data and the results were calculated by patient numbers but not implant numbers. Finally, seven articles were included for quantitative synthesis.

Figure 1. Flow chart of article screening
Qualify assessment of studies

The risk of bias in each study was summarized according to Cochrane RoB 2.0 (Figure 2). The randomization sequence generation process was not clearly addressed in two studies (Schrenk 1997 & Gomi 2015). Another two studies (Caruac 2017 & Hallstrom 2017) had more than 10% of participants lost follow-ups, which led to some concerns in the missing outcome data domain. There are also some concerns on the measurement of the outcomes in three of the studies (Schrenk 1997, Buchter 2004, Gomi 2015), because they did not mention about blinding of examiners. Finally, there is one study (Schrenk 1997) having high risk of bias on the selection of the reported result, because they made measurements on the probing depth, attachment level, and probing bone level but did not provide the results of them.

Figure 2. Risk of bias assessment for each study
Overall, five articles\(^{57, 59, 61, 63, 65}\) (Hallstrom 2012, Carcuac 2016, Chia 2019, Shibli 2019, Deeb 2020) were ranked as low risk of bias, four articles\(^{56, 60, 62, 64}\) (Schrenk 1997, Gomi 2015, Carcuac 2017, Hallstrom 2017) were ranked as some concerns, and one article\(^{60}\) (Schrenk 1997) was ranked as high risk of bias.

**Description of Studies**

The characteristics of the ten included studies are summarized (Table 1). A total of 596 implants in 355 patients were evaluated in the selected study cohorts. The mean ages of patients in each of the studies were from 51.5 to 69.9 years. The follow-up periods ranged from one month to 36 months. One study\(^{58}\) (Buchter 2004) did not mention exclusion criteria; while all the other studies excluded cases with history of compromised general health or antibiotics 3 or 6 months prior to beginning of the study. Only two studies excluded smokers from their sample populations\(^{61, 62}\) (Cha 2019, Gomi 2015), while one study only included current smokers\(^{59}\) (Deeb 2020). Among ten studies, three of them were looking at peri-implant mucositis\(^{59, 60, 63}\) (Schrenk 1997, Hallstrom 2012, Deeb 2020), the other seven studies were looking at peri-implantitis\(^{56-58, 61, 62, 64, 65}\) (Buchter 2004, Cha 2019, Gomi 2015, Carcuac 2016, Carcuac 2017, Hallstrom 2017, Shibli 2019).

The primary treatment for peri-implant mucositis\(^{59, 60, 63}\) (Schrenk 1997, Hallstrom 2012, Deeb 2020) was performed by scaling/debridement followed by rubber cup polishing, while the primary treatment for peri-implantitis was performed by subgingival scaling/debridement with or without open flap technique. Three studies\(^{56-58}\) (Buchter 2004, Carcuac 2016 & 2017) had used chlorhexidine irrigation for implant surface decontamination after debridement. Adjunct antibiotics intervention was administered either locally (three studies)\(^{58, 60, 61}\) (Schrenk 1997, Buchter 2004, Cha 2019) or systemically (seven studies)\(^{56, 57, 59, 62-65}\) (Hallstrom 2012, Gomi 2015,
Carcuac 2016, Carcuac 2017, Hallstrom 2017, Shibli 2018, Deeb 2020). However, in Cha’s study, they used both local and systemic antibiotics: the local minocycline ointment, Periocline, was the intervention of interest and used in the test group only, while systemic Amoxicillin were prescribed for both test and control groups 3 days postoperatively (Cha 2019).

**Synthesis on the results of BOP**

Table 2 shows the summarized treatment outcomes of included studies. All of the studies have the results on either post-treatment BOP or mean changes of BOP by percentages. The percentage was calculated by the number of BOP sites divided by the number of total measurement sites around the implants. In general, all studies showed reduction of BOP percentages around the implants after the treatments, and most of the studies revealed more reduction in ABX groups compared to control groups.
Table 1. The summary of characteristics of articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>No. of Patients and Implants</th>
<th>Peri-implant pathology and definition</th>
<th>Mean age (range)</th>
<th>Exclusion criteria</th>
<th>Primary treatment</th>
<th>Systemic/Local antibiotics (drug name) used in test group</th>
<th>Delivery method</th>
<th>Post-operative care</th>
<th>F/U time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schrenk G 1997</td>
<td>Split-mouth RCT</td>
<td>8 patients, 24 implants</td>
<td>Peri-implant mucositis (PD &gt;= 4mm with BOP, no peri-implant bone loss on radiographs)</td>
<td>62 (range 53-69)</td>
<td>(1) Systemic disorders (2) rheumatic heart disease, congenital heart defects, artificial heart valve or artificial joint replacements (3) Allergies to tetracycline or local anesthesia (4) Oral yeast infections (5) Taking systemic ABX within 3 months prior to baseline exam</td>
<td>Scaling, followed by rubber cup polishing</td>
<td>Local (tetracycline HCL)</td>
<td>ABX delivery by monolithic ethylene vinyl acetate fiber, then an isobutyl cyanoacrylate adhesive applied to secure the fiber. Total 1 time of ABX with a duration of 10 days</td>
<td>0.2% CHX rinse twice daily</td>
<td>4, 12 weeks</td>
</tr>
<tr>
<td>Buchter A 2004</td>
<td>RCT</td>
<td>28 patients, 48 implants</td>
<td>Peri-implantitis (radiographic evidence of bony defects &gt;50% length of implant)</td>
<td>55 (range 25-78)</td>
<td>NA</td>
<td>Scaling and irrigation with 0.2% CHX</td>
<td>Local (doxycycline, Atridox)</td>
<td>ABX delivery by injection of ABX solution via 23-gauge blunt cannula into the peri-implant pocket. Total 1 time of antibiotics</td>
<td>OHI</td>
<td>4 months</td>
</tr>
<tr>
<td>Cha JK 2019</td>
<td>RCT</td>
<td>46 patients, 46 implants</td>
<td>Peri-implantitis (PD=5 mm with BOP, and radiographic evidence of bone loss&gt;2 mm)</td>
<td>61.6 (range 40-84)</td>
<td>(1) pregnancy or lactation, (2) taking drugs that can affect periodontal disease (phenytoin, cyclosporin, calcium-channel blocker), (3) taking coumadin or NSAID, (4) diabetes mellitus (5) smoking, (6) uncontrolled systemic diseases, (8) allergic to TCN, (9) use CHX or any other type of mouth rinse (10) take ABX within the previous 3 months</td>
<td>OFD</td>
<td>Local (minocycline, Periocline)</td>
<td>Application of local ABX subgingivally, repeated with debridement at 1, 3, 6 months</td>
<td>Amoxicillin 500mg 3 times per day for 3 days</td>
<td>1, 3, 6 months</td>
</tr>
<tr>
<td>Hallstrom H 2012</td>
<td>RCT</td>
<td>46 patients, 46 implants</td>
<td>Peri-implant mucositis (PD &gt;= 4mm with BOP and/or suppuration on probing)</td>
<td>54.6 +/- 18.2 (test group)</td>
<td>(1) If &gt;=2.0mm bone loss from radiographs taken at the time of completion of the prosthetic restoration (2) pregnant or breast feeding (3) diagnosis of diabetes mellitus (4) allergic to erythromycin or other macrolides</td>
<td>Scaling followed by rubber cup polishing</td>
<td>Systemic (Azithromycin)</td>
<td>500mg daily on Day 1 and 250mg on Day 2-4. Total 5 days of antibiotics</td>
<td>OHI</td>
<td>1, 3, 6 months</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Implants</td>
<td>Condition</td>
<td>Methodology</td>
<td>Medication</td>
<td>Schedule</td>
<td>Outcomes</td>
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<tr>
<td>Deeb MA 2020</td>
<td>RCT</td>
<td>30 patients, 30 implants</td>
<td>Peri-implant mucositis (BOP, no peri-implant bone loss on radiographs)</td>
<td>51.5 +/- 2.31</td>
<td>Scaling followed by rubber cup polishing</td>
<td>Systemic (Azithromycin)</td>
<td>500mg daily on Day 1 and 250mg on Day 2-4. Total 5 days of antibiotics</td>
<td>0.12% CHX rinse twice daily for 14d post-operatively</td>
<td>6 and 12 weeks</td>
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<tr>
<td>Gomi K 2015</td>
<td>RCT</td>
<td>20 patients, 145 implants* (count from average No. of implants multiplied by No. of patients)</td>
<td>Peri-implantitis (PD&gt;= 4mm with BOP and radiographic evidence of bone loss)</td>
<td>67.6 (range 55-78)</td>
<td>Scaling</td>
<td>Systemic (Azithromycin)</td>
<td>500mg daily for 3 days before scaling. Total 3 days of antibiotics</td>
<td>OHI</td>
<td>1, 3, 6, 9, 12 months</td>
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<tr>
<td>Carcuac O 2016</td>
<td>RCT</td>
<td>100 patients, 179 implants</td>
<td>Severe peri-implantitis (PD&gt;= 6mm with BOP and/ or suppuration on probing, and radiographic evidence of bone loss&gt; 3mm)</td>
<td>66.3 +/- 13.6</td>
<td>Rubber cup polishing supragingivally, followed by OFD, bone recontouring, and decontamination with or without 0.2% CHX digluconate solution</td>
<td>Systemic (AMX)</td>
<td>1500mg daily started 3 days before surgical treatment, kept until post-treatment 7 days. Total 10 days of antibiotics</td>
<td>OHI prior to and after surgery, and 0.2% CHX rinse twice daily for 14d post-operatively</td>
<td>6, 12 months</td>
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<tr>
<td>Carcuac O 2017</td>
<td>RCT</td>
<td>100 patients, 179 implants</td>
<td>Severe peri-implantitis (PD&gt;= 6mm with BOP and/ or suppuration on probing, and radiographic evidence of bone loss&gt; 3mm)</td>
<td>66.3 +/- 13.6</td>
<td>Rubber cup polishing supragingivally, followed by OFD, bone recontouring, and decontamination with or without 0.2% CHX digluconate solution</td>
<td>Systemic (AMX)</td>
<td>1500mg daily started 3 days before surgical treatment, kept until post-treatment 7 days. Total 10 days of antibiotics</td>
<td>OHI prior to and after surgery, and 0.2% CHX rinse twice daily for 14d post-operatively</td>
<td>36 months</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Implants</td>
<td>Diagnostics</td>
<td>Prophylaxis</td>
<td>Follow-Up</td>
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<tr>
<td>Hallstrom H 2017</td>
<td>RCT</td>
<td>31 patients</td>
<td>31 Implants</td>
<td>Peri-implantitis (PD&gt;=5mm with BOP and/or suppuration on probing, and radiographic evidence of bone loss&gt;=3 mm) 69.9 (range 26-86)</td>
<td>OFD</td>
<td>Systemic (Azithromycin) 500mg at the day of surgery, and 250mg daily postoperatively for 4 days</td>
<td>12 months</td>
<td></td>
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</tr>
<tr>
<td>Shibli JA 2019</td>
<td>RCT</td>
<td>40 patients</td>
<td>40 implants</td>
<td>Peri-implantitis (PD&gt;5mm with BOP and/or suppuration on probing, and radiographic bone loss &gt;4mm, &gt;=50% peri-implant bone retained relative to implant length 58.5 +/- 11.1</td>
<td>Scaling</td>
<td>Systemic (MTZ and AMX) 400mg MTZ and 500mg AMX, three times a day. Total 14 days of antibiotics</td>
<td>3, 6, 12 months</td>
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</tbody>
</table>

ABX, antibiotics; AMX, amoxicillin; BOP, bleeding on probing; CHX, chlorhexidine; F/U, follow-up; MTZ, metronidazole NA, non-applicable; OFD, open flap debridement; OHI, oral hygiene instruction; PCN, penicillin; PD, probing depth; RCT, randomized clinical trial; TCN, tetracycline.
<table>
<thead>
<tr>
<th>Study/ Disease</th>
<th>Definition of BOP/SOP</th>
<th>Mean BOP reduction (%)</th>
<th>Definition of mean PD</th>
<th>PD reduction Mean +/- SD (mm)</th>
<th>Worst site PD reduction Mean +/- SD (mm)</th>
<th>Bone level changes radiographically Mean +/- SD (mm)</th>
<th>Microbiological findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local antibiotics</strong></td>
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<tr>
<td>Schrenk G 1997/ PIM</td>
<td>Percentage of BOP+ at 6 sites around implants</td>
<td>12-week: ABX 17% Control -15%</td>
<td>Mean of PDs measured at 6 sites at each implant</td>
<td>Not provided</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Buchter A 2004/ PI</td>
<td>Percentage of BOP+ at 4 sites around implants</td>
<td>4-month: ABX 27% Control 13%</td>
<td>Mean of PDs measured at 4 sites at each implant</td>
<td>4-month: ABX 1.15 +/- 0.23 Control 0.56 +/- 0.30</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cha JK 2019/ PI</td>
<td>Percentage of BOP+ at 4 sites around implants</td>
<td>6-month: ABX 49% Control 31%</td>
<td>Mean of PDs measured at 4 sites at each implant</td>
<td>6-month: ABX 2.68 +/- 1.73 Control 1.55 +/- 1.86</td>
<td>6-month: ABX 3.58 +/- 2.32 Control 2.45 +/- 2.13</td>
<td>6-month: ABX 0.72 Control 0.31</td>
<td>Number of red complex bacteria in both groups tended to decrease at 6-month after treatment. But no group differences in changes in red complex bacteria at all time points</td>
</tr>
<tr>
<td><strong>Systemic antibiotics</strong></td>
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<tr>
<td>Hallstrom H 2012/ PIM</td>
<td>Percentage of BOP+ at 4 sites around implants</td>
<td>1-month: ABX 44.6% Control 25.8% 3-month: ABX 44% Control 41.5% 6-month: ABX 55.3% Control 32.5%</td>
<td>Mean of PDs measured at 4 sites at each implant</td>
<td>1-month: ABX 0.9 Control 0.6 3-month: ABX 0.9 Control 0.7 6-month: ABX 0.9 Control 0.9</td>
<td>1-month: ABX 1.0 Control 0.9 3-month: ABX 1.1 Control 0.8 6-month: ABX 1.4 Control 0.8</td>
<td>NA</td>
<td>No study group differences in baseline bacterial counts for all species studied, nor differences in the changes of bacterial counts between baseline and the F/Us</td>
</tr>
<tr>
<td>Deeb MA 2020/ PIM</td>
<td>Percentage of BOP+ at 4 sites around implants</td>
<td>Baseline: ABX 15.7 +/- 3.9 Control 13.6 +/- 4.0 6-week: ABX 12.6 +/- 3.8 Control 12.0 +/- 4.1 3-month: ABX 10.1 +/- 3.1 Control 11.8 +/- 4.0</td>
<td>Mean of PDs measured at 4 sites at each implant</td>
<td>6-week: ABX 0.6 +/- 1.05 Control 0.2 +/- 0.85 3-month: ABX 0.75 +/- 1.05 Control 0.4 +/- 0.92</td>
<td>NA</td>
<td>NA</td>
<td>Only the ABX group had statistically significant reduction of Pseudomonas aeruginosa and Staphylococcus aureus from baseline to 12 weeks.</td>
</tr>
</tbody>
</table>

Table 2. Treatment outcomes of included articles
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>PI</th>
<th>Percentage of BOP+ at 6 sites around implants</th>
<th>Mean of PDs measured at 6 sites at each implant</th>
<th>Mean of PDs measured at 4 sites at each implant</th>
<th>Mean of PDs measured at 4 sites at each implant</th>
<th>Mean of PDs measured at 4 sites at each implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gomi K 2015/ PI</td>
<td></td>
<td></td>
<td>1-month: ABX 25.2% Control 8.4% 3-month: ABX 25.3% Control 5.9% 6-month: ABX 24.5% Control 6.1% 9-month: ABX 23.7% Control 5.3% 12-month: ABX 23.5% Control 5.9%</td>
<td>1-month: ABX 0.84 Control 0.23 3-month: ABX 0.93 Control 0.27 6-month: ABX 0.91 Control 0.23 9-month: ABX 0.94 Control 0.25 12-month: ABX 0.94 Control 0.13</td>
<td>6-month: ABX and CHX 3.03 +/-1.58 ABX only 3.49 +/- 1.54 CHX only 2.18 +/- 1.54 Control 1.95 +/- 1.81 12-month: ABX and CHX 2.80 +/- 1.87 ABX only 3.44 +/- 1.66 CHX only 2.16 +/- 1.79 Control 1.69 +/- 2.22</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Carcuac O 2016/ PI</td>
<td></td>
<td></td>
<td>No baseline data No BOP change data</td>
<td>NA</td>
<td>6-month: ABX and CHX 0.18 +/-1.15 ABX only 0.51 +/- 0.84 CHX only -0.69 +/- 1.32 Control -0.96 +/- 1.42</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Carcuac O 2017/ PI</td>
<td></td>
<td></td>
<td>No baseline data No BOP change data</td>
<td>36-month: ABX -3.00 +/- 2.24 Control -2.38 +/- 2.55</td>
<td>NA</td>
<td>36-month: ABX 0.32 +/- 1.35 Control -0.51 +/- 1.87</td>
<td>NA</td>
</tr>
<tr>
<td>Hallstrom H 2017/ PI</td>
<td></td>
<td></td>
<td>12-month: ABX 87.6% Control 86.7%</td>
<td>6-month: ABX 1.5 Control 1.3 12-month: ABX 1.7 Control 1.6</td>
<td>NA</td>
<td>12-month: ABX 0.6 Control 0.4</td>
<td>At 12-month, 25.8% individuals presented with no detectable level of nine bacterial species associated with periimplantitis. But no group differences in changes in bacterial load overtime compared to the baseline values</td>
</tr>
<tr>
<td>Shibli JA 2019</td>
<td>Percentage of BOP+ at 6 sites around implants</td>
<td>Baseline:</td>
<td>ABX 86.6 +/- 32.2</td>
<td>Control 85 +/- 18.3</td>
<td>3-month:</td>
<td>ABX 74.9 +/- 36.2</td>
<td>Control 74.9 +/- 30.6</td>
</tr>
</tbody>
</table>

ABX, antibiotics group; BOP, bleeding on probing; F/U, follow-up; NA, non-available; PD, probing depth; PI, peri-implantitis; PIM, peri-implant mucositis
Synthesis on the results of PD

PD have been assessed in all of the ten studies, but only nine studies reported the outcomes of PD, and six of them calculate the mean PD by implant numbers. Therefore, meta-analysis was conducted for those six studies to estimate the WMDPD between ABX and control treatments.

For the 3-month (short-term) effect, all three included studies used systemic antibiotics as adjunct treatments\(^62,63,65\) (Hallstrom 2012, Shibli 2019, Gomi 2015). In general, systemic antibiotics had beneficial effect on more PD reduction (WMDPD, 0.56; 95% CI, 0.22-0.90, p=0.001). But subgroup analysis revealed this beneficial effect was significant only in peri-implantitis but not in peri-implant mucositis (Figure 3) The quality of evidence was moderate (supplementary table 1).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abx Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2.1.1 Peri-implant mucositis</strong></td>
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<tr>
<td>Hallstrom 2012</td>
<td>0.9</td>
<td>0.72</td>
<td>22</td>
<td>0.7</td>
<td>1.03</td>
<td>24</td>
<td>27.7%</td>
<td>0.20 [-0.31, 0.71]</td>
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<tr>
<td>Subtotal (95% CI)</td>
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<td>0.20 [-0.31, 0.71]</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<td>Test for overall effect: Z = 0.77 (P = 0.44)</td>
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<tr>
<td><strong>2.1.2 Peri-implantitis</strong></td>
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<tr>
<td>Gomi 2015</td>
<td>0.93</td>
<td>0.66</td>
<td>76</td>
<td>0.27</td>
<td>0.26</td>
<td>69</td>
<td>64.5%</td>
<td>0.66 [0.50, 0.82]</td>
</tr>
<tr>
<td>Shibli 2019</td>
<td>1.4</td>
<td>2.31</td>
<td>20</td>
<td>0.4</td>
<td>1.21</td>
<td>20</td>
<td>7.8%</td>
<td>1.00 [-0.14, 2.14]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67 [0.51, 0.83]</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 8.22 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>118</td>
<td>113</td>
<td>100.0%</td>
<td>0.56 [0.22, 0.90]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.04; Chi² = 3.26, df = 2 (P = 0.20); I² = 39%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.25 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 2.93, df = 1 (P = 0.09), I² = 65.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Short-term (3 months) changes on probing depth (all systemic antibiotics)

For the 6-month effect, meta-analysis of six studies\(^57,61-65\) (Cha 2019, Carcuac 2016, Gomi 2015, Hallstrom 2012, 2017, Shibli 2019) showed the ABX groups had significantly more PD reduction compared to control groups (WMDPD, 0.82; 95% CI, 0.50-1.14, p<0.00001), especially for peri-implantitis (WMDPD, 0.83; 95% CI, 0.52-1.13, p<0.0001) (Figure 4a). The quality of
evidence was low due to high heterogeneity of studies (supplementary table 1). Subgroup analysis according to whether local or systemic antibiotics was used showed both types of antibiotics had beneficial effect on reducing more probing depth (Figure 4b). For the 12-month effect, all of the four studies57, 62, 64, 65 (Carcuac 2016, Gomi 2015, Hallstrom 2017, Shibli 2019) were peri-implantitis cases using systemic antibiotics as adjunct treatment. The meta-analysis also showed a better result from ABX groups in PD reduction compared to control groups (WMDPD, 0.92; 95% CI, 0.51-1.32, p< 0.0001) (Figure 5). The quality of evidence was low due to high heterogeneity (supplementary table 1).

---

**Figure 4 (a).** Six months changes on probing depth, subgroup by disease
Figure 4 (b). Six months changes on probing depth, subgroup by antibiotics

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abx Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cha 2019</td>
<td>2.68</td>
<td>1.73</td>
<td>24</td>
<td>1.55</td>
<td>1.86</td>
<td>22</td>
<td>6.1%</td>
<td>1.13 [0.09, 2.17]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td></td>
<td></td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td>6.1% 1.13 [0.09, 2.17]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 2.13$ ($P = 0.03$)

3.3.2 Systemic antibiotics

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Abx Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcuac 2016 (CHX)</td>
<td>3.03</td>
<td>1.58</td>
<td>47</td>
<td>2.18</td>
<td>1.54</td>
<td>45</td>
<td>13.8%</td>
<td>0.85 [0.21, 1.49]</td>
<td></td>
</tr>
<tr>
<td>Carcuac 2016 (Non-CHX)</td>
<td>3.49</td>
<td>1.54</td>
<td>46</td>
<td>1.95</td>
<td>1.81</td>
<td>35</td>
<td>10.7%</td>
<td>1.54 [0.79, 2.29]</td>
<td></td>
</tr>
<tr>
<td>Gomi 2015</td>
<td>0.91</td>
<td>0.84</td>
<td>76</td>
<td>0.23</td>
<td>0.26</td>
<td>69</td>
<td>44.4%</td>
<td>0.68 [0.48, 0.88]</td>
<td></td>
</tr>
<tr>
<td>Hallstrom 2012</td>
<td>0.9</td>
<td>1.25</td>
<td>22</td>
<td>0.5</td>
<td>1.22</td>
<td>21</td>
<td>10.9%</td>
<td>0.40 [-0.34, 1.14]</td>
<td></td>
</tr>
<tr>
<td>Hallstrom 2017</td>
<td>1.5</td>
<td>1.19</td>
<td>15</td>
<td>1.3</td>
<td>1.22</td>
<td>16</td>
<td>8.7%</td>
<td>0.20 [-0.65, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Shibli 2019</td>
<td>3.1</td>
<td>2.25</td>
<td>20</td>
<td>2.1</td>
<td>1.15</td>
<td>20</td>
<td>5.4%</td>
<td>1.00 [-0.11, 2.11]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>226</td>
<td></td>
<td></td>
<td>206</td>
<td></td>
<td></td>
<td></td>
<td>93.9% 0.75 [0.45, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\tau^2 = 0.04; \chi^2 = 7.35, df = 5$ ($P = 0.20$); $I^2 = 32%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for overall effect: $Z = 4.92$ ($P < 0.00001$)

Figures, Long-term (12 months) changes on probing depth (all systemic antibiotics and peri-implantitis)

Radiographic bone level

Four studies were included\textsuperscript{57, 61, 64, 65} (Cha 2019, Carcuac 2016, Hallstrom 2017, Shibli 2019); three studies\textsuperscript{57, 64, 65} (Carucuac 2016, Hallstrom 2017, Shibli 2019) had 12-month outcomes and one study (Cha 2019) had a 6-month outcome. The meta-analysis showed more gain of bone in favor of using adjunct ABX (WMDRDBG, 0.64; 95% CI, 0.05-1.23, $p = 0.03$) (Figure 6). The quality of evidence was very low due to inconsistency and high heterogeneity (supplementary table 1).
**Figure 6.** Outcome of radiographic bone gain (6 to 12 months) (all peri-implantitis)

**Supplementary Table 1**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Risk with No antibiotics</th>
<th>Risk with Adjunct Antibiotics</th>
<th>Relative effect (95% CI)</th>
<th>N of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probing depth: 3M follow up</td>
<td>The mean probing depth: 3M follow up was 0 mm</td>
<td>MD 0.66mm (0.48 higher to 0.72 higher)</td>
<td>-</td>
<td>289 (5 RCTs)</td>
<td>MODERATE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probing depth: 6M follow up</td>
<td>The mean probing depth: 6M follow up was 0 mm</td>
<td>MD 0.77mm (0.43 higher to 1.11 higher)</td>
<td>-</td>
<td>386 (6 RCTs)</td>
<td>LOW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probing depth: 12M follow up</td>
<td>The mean probing depth: 12M follow up was 0 mm</td>
<td>MD 0.97mm (0.48 higher to 1.47 higher)</td>
<td>-</td>
<td>297 (4 RCTs)</td>
<td>LOW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone level: 6-12 M follow up</td>
<td>The mean bone level: 6-12 M follow up was 0 mm</td>
<td>MD 0.51mm (0.13 lower to 1.15 higher)</td>
<td>-</td>
<td>198 (4 RCTs)</td>
<td>VERY LOW</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; MD: Mean difference

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

**Treatment success**
Four studies\textsuperscript{56, 61, 64, 65} (Cha 2019, Carcuac 2017, Hallstrom 2017, Shibli 2019) provided comparison of treatment success of peri-implantitis between ABX and control groups. Their definition of treatment success is similar, and all included PD equal and/or less than 5mm, no bleeding or suppuration on probing, and no or less than 0.5 mm further bone loss at 6 months or 12 months after the treatment. Therefore, meta-analysis can be conducted. It showed the ABX group presented a significantly greater treatment success when compared to the control group (WPOR, 1.74; 95% CI, 1.03- 2.94, p=0.04) (Figure 7). The quality of evidence was moderate (supplementary table 2).

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Study or Subgroup & Abx Events & Control Events & Total Events & Weight & M-H, Random, 95% CI & \hline
Cha 2019 & 16 & 24 & 8 & 22 & 18.6\% & 3.50 [1.04, 11.79] & \hline
Subtotal (95\% CI) & 24 & 22 & 8 & 3.50 [1.04, 11.79] & \hline
Total events & 16 & 8 & 3.50 [1.04, 11.79] & \hline
Heterogeneity: Not applicable
Test for overall effect: Z = 2.02 (P = 0.04) & \hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Study or Subgroup & Abx Events & Control Events & Total Events & Weight & M-H, Random, 95% CI & \hline
Carcuac 2017 & 39 & 68 & 27 & 53 & 52.6\% & 1.30 [0.63, 2.67] & \hline
Hallstrom 2017 & 7 & 15 & 4 & 16 & 11.9\% & 2.63 [0.57, 12.00] & \hline
Shibli 2019 & 13 & 20 & 11 & 20 & 16.9\% & 1.52 [0.43, 5.43] & \hline
Subtotal (95\% CI) & 103 & 89 & 81.4\% & 1.48 [0.83, 2.65] & \hline
Total events & 59 & 42 & \hline
Heterogeneity: Tau\textsuperscript{2} = 0.00; Chi\textsuperscript{2} = 0.68, df = 2 (P = 0.71); I\textsuperscript{2} = 0\% & \hline
Test for overall effect: Z = 1.33 (P = 0.18) & \hline
Total (95\% CI) & 127 & 111 & 100.0\% & 1.74 [1.03, 2.94] & \hline
Total events & 75 & 50 & \hline
Heterogeneity: Tau\textsuperscript{2} = 0.00; Chi\textsuperscript{2} = 2.24, df = 3 (P = 0.52); I\textsuperscript{2} = 0\% & \hline
Test for overall effect: Z = 2.07 (P = 0.04) & \hline
Test for subgroup differences: Chi\textsuperscript{2} = 1.56, df = 1 (P = 0.21), I\textsuperscript{2} = 35.9\% & \hline
\end{tabular}
\end{table}

\textbf{Figure 7.} Meta-analysis on treatment success (6 to 12 months) (all peri-implantitis)
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>№ of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with No antibiotics</td>
<td>Risk with Adjunct antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment success</td>
<td>450 per 1,000</td>
<td>588 per 1,000 (458 to 707)</td>
<td>OR 1.74 (1.03 to 2.94)</td>
<td>238 (4 RCTs)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

**GRADE Working Group grades of evidence**

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**Supplementary Table 2**
Discussion

Summary of the main finding

In the present study, we found that adjunct use of antibiotics provides significant clinical benefits in the treatment of peri-implant diseases, including PD reduction, radiographic bone gain and treatment success in the meta-analysis. This additional clinical benefit with antibiotics is especially significant when applied to peri-implantitis cases but not as much to peri-implant mucositis cases based on the subgroup analysis.

Similar to the progression from gingivitis to periodontitis, peri-implant mucositis is the precursor of peri-implantitis\(^66\), and it is usually considered to be an inflammatory lesion confined to the soft tissue surrounding implants without the loss or continuing loss of supporting bone\(^67\); whereas peri-implantitis is characterized by the inflammation found in the peri-implant soft tissue that leads to progressive loss of supporting bone\(^68\). Yet, it is challenging to define a clear cut between these two diseases clinically due to the difficulty of detecting the initiation of the pathological bone loss. Therefore, the case definitions of peri-implant mucositis and peri-implantitis varies in between studies\(^69\)–\(^71\) and is the reason we included both diseases in our study to provide a more comprehensive assessment.

Local and systemic antibiotics

Local controlled delivery of antibiotics has been used to treat peri-implant diseases in order to maintain the high concentrations in the defect\(^60\), \(^72\), \(^73\). Three studies evaluating the effect of different type of local antibiotics\(^58\), \(^60\), \(^61\) were included in our review, but two were excluded from the meta-analysis due to the lack of quantitative data\(^60\) or missing information of the implant
numbers. Thus, our meta-analysis cannot draw firm conclusion for local antibiotics in the treatment of peri-implant diseases since only one study fits our stringent criteria to evaluate the true adjunct effect of antibiotic for quantitative analysis. Although these three RCTs cannot be analyzed together, we can still see a trend from the original studies that local antibiotics appeared to be effective in the treatment of peri-implantitis, but not as much in peri-implant mucositis. This finding is also in line with other systematic review and controlled trials.

Pertaining to the use of adjunct systemic antibiotics in the treatment of peri-implant diseases, the subgroup analysis provides a mean difference from 0.56 to 0.92 mm in PD reduction, favoring ABX group at all follow up time points (Figure 3, 4b, 5), but the benefit in radiographic bone gain (Figure 6) and treatment success (Figure 7) is not significant. Specifically, for peri-implantitis, the current meta-analysis proved that significant more PD reduction at 1 year can be achieved when systemic antibiotics were applied (Figure 5). It is noteworthy that Carcuac study highlights that the clinical benefits of systemic antibiotic were only limited to implants with modified surfaces and the benefits fail to sustain long-term. This could be related to the fact modified rough implant surface harbors biofilm and bacteria reside in areas possibly sheltered from mechanical debridement, therefore, systemic antibiotics could have a role in this scenario. There is only one study about treating peri-implant mucositis with systemic antibiotics in our analysis, thus solid conclusion cannot be drawn for this perspective.

Collectively, adjunct antibiotics showed convincing results in PD reduction, radiographic bone gain and treatment success in the present meta-analysis. Nonetheless, we found that Cha study, the only included localized antibiotic study, had significant impact on the overall result. Without Cha study, the analysis of systemic antibiotics alone failed to define significant clinical
benefits on radiographic bone gain and treatment success (Figure 6 & 7). It should be noted that although the focus of Cha study is the effect of repeated use of local minocycline ointment, they also applied systemic antibiotic to both treatment groups. As a consequence, we could not determine if the superior outcome was from the combined antibiotic therapy or the true effect of the local antibiotic. Based on this review’s analysis, it appears that adjunct antibiotics are potentially clinically beneficial for the treatment of peri-implant diseases, yet the most efficient kind of antibiotic and type of delivery system remains unclear.

**Microbiology**

Since peri-implant diseases are bacteria induced diseases, the microbiological result can be a good treatment outcome indicator. From culture-based techniques\(^\text{20, 76, 78-80}\) to cultivation-independent investigations\(^\text{81, 82}\), peri-implant diseases have been shown to be consisted of predominantly Gram-negative anaerobic microflora, which is similar to, but less complex than chronic periodontitis. Predominant microbiota in peri-implant mucositis is similar to peri-implantitis and has been confirmed by a study using the checkerboard DNA–DNA hybridization technique\(^\text{83}\).

The only local antibiotic study with microbiological data in this review revealed no significant intergroup differences in the reduction of red complex bacteria at all time points\(^\text{61}\). The post-op systemic antibiotic applied to both ABX and control groups may have potentially masked the contribution made by local minocycline. Two studies using 5-day-course systemic azithromycin combined with non-surgical therapy to treat peri-implant mucositis presented inconsistent microbiological results\(^\text{59, 63}\). One study failed to detect any advantages from the use of antibiotics\(^\text{63}\). In contrast, the other study showed significant reduction of *Pseudomonas*
*Enterococcus aeruginosa* and *Staphylococcus aureus*, two bacteria closely linked to implant failure\(^{64}\), only in the ABX group at one year follow up\(^{59}\) (Deeb et al., 2020). The variance in results between these two studies could be caused by the difference in patient populations studied. Deeb’s study only included smokers, and smoking has been proven to influence the composition of subgingival microbiota\(^{85}\). With regard to the use of systemic antibiotics for the treatment of peri-implantitis, two studies using systemic azithromycin had different findings\(^{62,64}\). Gomi et al. found that common periodontal pathogens were more effectively reduced in the ABX group, especially *Porphyromonas gingivalis*, *Treponema denticola*, and *Prevotella intermedia*, but the pathogen gradually increased at 6 months. In the other study, the statistical analysis of checkerboard DNA-DNA hybridization failed to identify different total bacterial load between groups at any time point without showing the information of individual bacteria\(^{64}\). Shibli et al. echoed Gomi’s finding with a combination of systemic antibiotics (*metronidazole* + *amoxicillin*); in the study, red complex species are still in significantly lower proportions at 12 months compared to baseline in the ABX group, but control group showed no difference from baseline\(^{65}\).

The inconsistent microbiological results among studies could be due to differences in microbial analysis methods and the varied ways biofilm is collected. Although most of the included studies collected subgingival biofilm from the deepest pocket around implant with paper points, there is one study that used gracey curette instead\(^{65}\). The microbiological analysis also varied in between studies, from PCR, real-time PCR to checkerboard DNA-DNA hybridization. All the microbiological methods in the selected studies were “close-ended” techniques, with limited numbers of targeted taxa detected. In the future, the “open-ended” sequencing-based techniques might be applied for microbiological evaluation to provide an unbiased assessment of the whole bacterial profile in peri-implant lesions.
Strength and Limitation

To our knowledge, all available literature does not report quantitative data on the use of adjunct antibiotics for peri-implant diseases. Our current systematic review and meta-analysis aimed to evaluate the overall antimicrobial effect of local or systemic antibiotics on peri-implant diseases, and we were able to quantify the clinical outcome using subgroup analysis and sensitivity test.

The results should be interpreted with caution due to the limitations in the current review: 1. Due to the lack of an established standard antibiotics regimen for peri-implant mucositis and peri-implantitis and well-executed RCTs, the quality of evidence for the outcome was downgraded mostly due to high heterogeneity and risk of bias. 2. BOP was presented differently among studies which cause difficulty in performing meta-analysis, thus, this current review failed to quantify the effect of antibiotics on BOP reduction. Consequently, in order to draw a more precise conclusion for this topic, more well-designed RCTs for both local and systemic antibiotics in the adjunct use of peri-implant treatments should be conducted in the future.

Conclusion

The results of this meta-analysis support that the use of adjunct antibiotics provides additional benefit in the treatment of peri-implant diseases in all clinical assessments we analyzed, and this effect is especially significant in peri-implantitis cases. The most consistent advantage is the PD reduction, with almost 1mm more improvement favoring adjunct antibiotic group at one year follow up.
References

12. Tonetti M, Palmer R. Clinical research in implant dentistry: study design, reporting and outcome measurements: consensus report of Working Group 2 of the VIII European


