# Adjunctive therapies for the nonsurgical treatment of peri-implant diseases: systemic review and meta-analysis

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**Research article**

**Keywords:** adjunctive therapies, mechanical debridement, non-surgical treatment, pe-ri-implantitis

**Posted Date:** May 27th, 2020

**DOI:** https://doi.org/10.21203/rs.3.rs-15961/v4

# Abstract

Background Peri-implant diseases are mainly caused by biofilms around the implant and may lead to implant failure. Non-surgical mechanical debridement with different adjunctive therapies has being applied in the treatment of peri-implant diseases. This systematic review aims to figure out whether one adjunctive therapy is superior to any other.

Methods Two independent authors screened the literature via the MEDLINE, Cochrane Library and Science Direct. Only clinical randomized controlled trials (RCTs) that compared the efficacy of adjunctive therapies in the treatment of peri-implant diseases with non-surgical mechanical debridement (MD) were included in this review. The studies selected were published before June 2020. Comparisons of clinical outcomes were estimated using meta-analysis

Results: A total of eighteen RCTs met the inclusion criteria, of which 13 articles were included in the meta-analysis. The following adjunctive interventions were compared in the included studies: modifying the prosthesis; air abrasive; photodynamic therapy; local antibiotics; systemic antibiotics; probiotics. Statistically significant difference was observed between MD with photodynamic therapy and MD alone at 3 months follow-up ( $P < 0.01$). There is no statistical difference between MD with chlorhexidine and MD alone in the treatment of peri-implant diseases at 3 months follow-up ( $P = 0.84$), so is MD with probiotics and MD alone ( $P = 0.96$), and so is systemic antibiotics and MD alone ( $P = 0.47$).

Conclusion. MD adjunct with PDT is an effective treatment for peri-implant mucositis. However, there is still no effective non-surgical treatment for peri-implantitis.


# Background

Peri-implant diseases include Peri-implant mucositis and peri-implantitis. Peri-implant mucositis is a reversible inflammatory response of the mucosa adjacent to the implant without bone loss. Peri-implantitis, instead, has been defined as an inflammatory process that affects the soft tissues surrounding an osseointegrated implant in function with concomitant loss of supporting marginal bone[1, 2]. Peri-implant diseases are maily caused by biofilms around the implant in susceptible individuals, affecting inflammation of peri-implant tissues. The incidence of peri-implant diseases is not low. According to a review, peri-implant mucositis occurs in approximately 80% of patients (50% of the implant), and in 28-66% of the patients (12-40% of the implant), the disease translates into Peri-implantitis[3].

Inflammation of peri-implant tissues is mainly caused by peri-implant biofilms in susceptible individuals[4]. Decontamination of the implant surface and eradication of the biofilm and endotoxins are the major challenge in the treatment of peri-implant diseases[5]. Mechanical debridement (MD) is recognized as indispensable, basal procedure in the non-surgical treatment. MD can improve outcomes, such as clinical attachment level (CAL) gain and pocket probing depth (PPD) reduction[6]. However, in some clinical studies, several weeks after MD, there was a recurrence of the disease in a significant percentage of patients[7, 8]. The complete resolution after MD is still not frequent event.

To assist MD in treating peri-implant diseases, researchers have applied various adjunctive therapies to enhance clinical outcomes. These adjunctive therapies include: 1) air abrasive; 2) photodynamic therapy (PDT); 3) local drug delivery (e.g. chlorhexidine, chloramine or probiotic); 5) systemic antibiotics; 6) modifying the prosthesis; 7) the combination of some of the above therapies. Many literatures compared these adjunctive therapies, and the results were diverse[9-42]. There is no consensus regarding the optimal protocol for non-surgical treatment of peri-implant diseases. A systematic comparison of different adjunctive therapies for the peri-implant diseases has not yet been undertaken. Henceforth, the present systematic review aims to figure out whether one adjunctive therapy of non-surgical decontamination is superior to any other.

# Methods

This systematic review was designed and conducted in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2015 statement[43].

## Inclusion criteria

Only clinical randomized controlled trials (RCTs) that compared the effectiveness of MD with or without adjunctive therapy for non-surgical treatment of peri-implant diseases published before June 2020 were considered eligible for inclusion in this review. And the language was limited to English.

## Exclusion criteria

Studies requiring an additional surgical technique, such as flap surgery, guided bone regeneration or any grafting procedure were excluded. Studies with insufficient data were also excluded.

## Screening process

Searches were performed in MEDLINE (PubMed), Cochrane Library and Science Direct databases until June 2020. For the PubMed library, the key terms used were as follows: (((((dental implant [MeSH Terms]) OR oral implant [MeSH Terms]) AND therapy) OR treatment) AND peri-implantitis). On the other side, for Cochrane Library and Science Direct the key terms used were: *(Title, Abstract, Keywords):* dental implant AND therapy OR treatment AND peri-implantitis. The screening in such databases “humans” and “clinical trials” were applied as restricted studies. The electronic search was complemented by manual searches of the reference lists of the selected publications, including *Journal of Dental Research, Journal of Clinical Periodontology, Journal of Periodontology* and the *International Journal of Periodontics and Restorative Dentistry*, from January 2019 up to February 2020

A total of two calibrated independent reviewers (YHX & YCQ) (*Kappa* 0.96) screened all titles/abstracts and the full texts of the articles were retrieved by the search strategy. The articles that fulfilled the eligibility criteria were included in the present study. The reviewers searched the reference lists of the included articles for additional relevant publications. Any discrepancies between the two reviewers were resolved following additional discussion with a third reviewer (HYY).

## Quality assessment

A quality assessment of the included studies (RCTs) was done following the recommendations for systematic reviews of interventions of the Cochrane collaboration[44], focusing on the following criteria: random sequence generation and allocation concealment (both accounting for selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment. (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), or other possible causes of bias.

## Data extraction and statistical analysis

Two independent reviewers (YHX & HLJ) extracted the data. Disagreements between the two reviewers were resolved following additional discussion with a third reviewer (HYY). A standardized data extraction form was used to collect the following data: 1) author, year; 2) number of patients; 3) number of implants; 4) mean age of the patients; 5) years of implant in function; 6)

smoker; 7) history of periodontitis; 9) length of follow-up; 10) adjunctive treatments; 11) clinical outcomes, including method of assessment and time intervals..

Meta-analysis was performed using the Review Manager software (Review Manager version 5.3; The Cochrane collaboration, Copenhagen, Denmark). The statistical heterogeneity among the RCTs selected for meta-analysis was assessed utilizing the DerSimonian–Laird estimate $\tau^2$ for inter study variance. Because each clinical outcome was evaluated in a similar way, preferring smaller values, so meta-analysis could be performed together. The meta-analysis was performed to investigate on a standardized mean difference between the clinical outcomes in the groups of adjunctive therapies compared with MD.

# Results

The initial search yielded 1698 publications found in PubMed Library, 1042 in Cochrane Library and 586 in Science Direct. Four more publications were identified by manual search. After removing duplicate studies, there were 2723 publications of potential interest to screen. After excluding articles based on their titles and abstracts, 39 studies were left for full-text assessment. Following a discussion after full-text analysis, 18 studies were included for systematic review[9, 10, 12, 13, 16, 17, 19, 20, 23, 24, 26, 31-36, 41]. The process of identification of the included studies from the initial yield is described in Fig.1. The numbers of patients, mean age, implant data and adjunctive treatments are listed in Table 1.

Quality assessment

Summarizing the risk of bias for each study, only six studies were considered at low risk of bias[17, 20, 23, 33, 34, 36], seven were at unclear risk[10, 14, 16, 19, 31, 35, 41], and five studies were considered at high risk of bias[9, 13, 24, 26, 32]. Results of the quality assessment of RCTs are listed in Table 2, following the recommendations[44]. The difference of the assessment results was low (*Kappa* 0.92) and the consent was reached by discussion.

Meta-analysis

13 articles were included in the meta-analysis. Meta-analysis was carried out, including data reporting mean values of pocket probing depth (PPD), bleeding of probing (BOP), clinical attachment loss (CAL) and plaque index (PI), comparing the outcomes of MD combined with PDT, chlorhexidine, systemic antibiotics or probiotics with MD alone. The follow-up time for each study was not the same, so only the most comprehensive results reported at 3 months and 6 months were included. For meta-analysis, summary measures of each included study were used only, because individual data could not be extracted from the studies. Subgroup analyses of these studies concerning different clinical outcomes were performed.

Because of different measurement methods, standardized mean difference was investigated to compare the clinical outcomes in the groups of adjunctive therapies and MD. Standardized mean difference of clinical outcomes (BOP, CAL, PPD) of 0.60 ($CI_{95\%}$ -1.20; 2.40) between group MD with PDT and group MD alone was found significantly different from 0 ($P < 0.01$). Standardized mean difference of clinical outcomes (BOP, PPD) of -0.01 ($CI_{95\%}$ -0.24; 0.22) between group MD with chlorhexidine treatment and group MD alone was found no significant difference from 0 ($P = 0.84$). Standardized mean difference of clinical outcomes (BOP, PPD) of -0.02 ($CI_{95\%}$ -0.32; 0.29) between group MD with systemic antibiotics treatment and group MD alone was found no significant difference from 0 ($P = 0.47$). Standardized mean difference of clinical outcomes (BOP, PI, PPD) of -0.26 ($CI_{95\%}$ -0.54; 0.03) between group MD with probiotics treatment and group MD alone was found no significant difference from 0 ($P = 0.96$). Fig.2-5 depict the forest plot of standardized mean differences of clinical outcomes between MD with adjunctive therapies and MD alone.

# Discussion

PDT involves interactions between a light source and a photosensitizer in an aerobic environment. This results in the generation of free oxygen radicals that damage target cells such as bacterial cells[45]. At present, the light sources of PDT are mainly included diode laser, argon laser, Er:YAG laser (ERL) and light emitting diode (LED)[12-14, 46, 47]. Studies have indicated that nonsurgical periodontal treatment with an PDT significantly improve clinical outcomes as evidenced by PPD reduction and gain of CAL[46, 48]. PDT has also been reported to kill pathogenic microbes associated with the etiology of periodontal and peri-implant disease such as *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), Prevotella intermedia, and Porphyromonas gingivalis (P. gingivalis)[49]*. A total of 7 articles included in this study were about PDT, three of which were about peri-implant mucositis[14, 17, 19] and four were about peri-implantitis[13, 16, 20, 41]. The follow-up time of three literatures on peri-implant mucositis was only three months, probably because inflammation had improved significantly within three months after treatment, and no longer observation time was required. These three literatures all concluded that MD with PDT could significantly reduce clinical signs of inflammation like CAL and PPD compared with MD alone. For peri-implantitis, the short-term effect of MD adjunct PDT was significant, but the long-term effect was comparable to MD alone. As the meta-analysis shown in Fig.2. Compared with peri-implant mucositis, peri-implant inflammation can lead to defects of bone tissues around the implant and contamination of the implant surface, making treatment more difficult[50]. All of the 7 studies applied PDT only once, and there is no research on whether repeated use of PDT will improve or prolong its effect on the treatment of peri-implantitis.

Air abrasive devices have been shown to be a feasible treatment option in periodontal care because it has the potential to effectively erase biofilms[47]. Amino acid glycine particles had been proved to be effective in removal of the biofilm[51]. One of the included RCTs was about the effect of air abrasive as an adjunct in the treatment of peri-implant diseases[10], which found that adjunctive air abrasive treatment seemed to have a limited beneficial effect as compared with MD alone. Professional MD can effectively remove biofilms where the instruments can reach, thus the adjunctive effect of air abrasive may be limited. The evidence available does not allow for any conclusive statements on the clinical application of air polishing for the management of peri-implant diseases.

Four articles included in this review were about the adjunct effect of chlorhexidine in the treatment of peri-implant diseases. Chlorhexidine is a commonly used topical drug. As shown in Fig.3, compared with MD alone, MD with chlorhexidine have a limited beneficial effect at 3 months following treatment. An included article reported the adjunctive effect of chloramine and found that chloramine could not improve the clinical outcomes of peri-implant diseases[31]. The effects of probiotic *Lactobacillus reuteri* in combination with MD were evaluated in implants with peri-implantitis, and no clinical differences between probiotic and placebo treatments were observed over time[35, 36] (Fig.4). Compared with chlorhexidine, Minocycline microspheres as an adjunct to MD treatment of incipient peri-implantitis lesions demonstrated improvements in PPD and BI that were sustained over 6 months[28, 29]. The state of the topical drugs, the concentrations of the topical drugs and the way of delivering topical drugs may affect the effectiveness of the drugs. Dental water jet rinse mixed with chlorhexidine gel might supplement the response to nonsurgical treatment for peri-implantitis in a short term by reducing PPD[32]. Studies have found that repeated chlorhexidine chips application might resolve marginal peri-implant inflammation in terms of BOP better than chlorhexidine gel, and PPD was more reduced with 0.65 ± 0.40 mm [30, 38]. The efficacy of a single dose is limited, repeated application of local drugs can prolong the effectiveness. However, the frequent use of antibiotics causes bacterial resistance in the subgingival biofilm[52]. There is no consensus on how to deliver topical drugs in the treatment of peri-implant diseases. Therefore, further studies are warranted.

Two articles included in this study were about systemic antibiotics, one was about peri-implant mucositis[34] and the other was about periimplantitis[33]. Both literatures found that systemic antibiotics had limited effect in the treatment of peri-implant diseases, as the standardized mean difference of clinical outcomes (BOP, PPD) between group MD with systemic

antibiotics treatment and group MD alone was found no significant difference from 0 ($P$ = 0.47) (Fig. 5). This may because the amount of systemic antibiotics that can reach the area around the implant is little, so the local antibacterial effect is not significant. Tada et al.[37] evaluated the adjunctive clinical efficacy of systemic antibiotics in the treatment of peri-implantitis with MD and probiotic. They founded that the PPD was significantly lower in the test group. This suggests that we can combine multiple treatments when treating peri-implantitis, which may increase the clinical effect.

Tapia et al.[9] found that modifying the contour of the prostheses after mechanical debridement significantly improved the clinical outcomes of peri-implant mucositis. This conclusion was correlated to the inclusion criteria of the study, which required the included patients to have at least one implant supported restoration with an inappropriate prosthesis design or contour that made difficult oral hygiene access to the neck of the implant. Implant supported prosthesis design is important to promote accessibility to oral hygiene around implants[53], which suggests a way to treat peri-implantitis.

Enamel matrix derivatives have been employed successfully in the management of periodontal diseases and in particular bone loss associated with periodontitis[54]. Kashefimehr et al.[39] studied the effects of enamel matrix derivative on non-surgical management of peri-implant mucositis, and they found that MD in conjunction with enamel matrix derivative , air abrasive and 0.12% chlorhexidine mouthwash significantly improved BOP and PPD at 3 months following the treatment. In the group with enamel matrix derivative, PPD reduced from 5.40 ± 1.79 mm to 4.66 ± 1.95 mm. More studies are required to prove the efficacy of enamel matrix derivative in longer-terms.

In summary, our study compared several therapies as adjuncts to the non-surgical MD treatment of peri-implant lesions. Our results indicate that PDT is a promising adjunct method for the treatment of peri-implant mucositis. Modifying the prosthesis also has significant effects in the treatment of peri-implant mucositis. However, from the perspective of long-term efficacy, there is still no effective non-surgical treatment of peri-implantitis. The combination of multiple treatments for peri-implantitis may improve the clinical outcomes. Further studies are warranted.

## Conclusion

MD adjunct with PDT is an effective treatment for peri-implant mucositis. However, there is still no effective non-surgical treatment for peri-implantitis.

## List Of Abbreviations

RCTs: Randomized controlled trials

MD: Mechanical debridement

PDT: Photodynamic therapy

CAL: Clinical attachment level

PPD: Pocket probing depth

BOP: Bleeding of probing

PI: Plaque index

ERL: Er:YAG laser

LED: Light emitting diode

# Declarations

### Ethics approval and consent to participate

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

### Consent for publication

Not applicable

### Availability of data and materials

All data are fully available without restriction.

### Competing interests

The authors declare that they have no competing interests


### Funding

Not applicable


### Authors' contributions

Yuhan Xiao and Haiyang Yu had made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. Yichun Qin had been involved in drafting the manuscript or revising it critically for important intellectual content. Haiyang Yu gave final approval of the version to be published. Haiyang Yu agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.


### Acknowledgements

Not applicable.


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# Tables

Table 1. Description of included studies.

| Author, year | Patients (*n*) | Age (mean ± SD, years) | | Implants (*n*) | | Years of implant in function (mean ± SD) | | Current smokers | | History of periodontitis, *(n)* | | Follow-up (months) | Adjunctive treatments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T | C | T | C | T | C | T | C | T | C | | |
| Tapia et al. 2019 | 45 | 60.9±9.9 | 61.2±12.9 | 73 | 72 | 10.2±5.4 | 9.1±4.8 | 1 | 1 | - | - | 6m | Modifying the prosthesis |
| Ji et al. 2012 | 24 | 46.2 | 41.3 | 17 | 16 | - | - | 0 | 0 | 4 | 4 | 3m | Air abrasive |
| Arısan et al. 2015 | 10 | - | - | 24 | 24 | - | - | - | - | - | - | 6m | Photodynamic therapy |
| Aimetti et al. 2018 | 220 | 58.1±10.1 | 56.8±10.2 | 110 | 110 | 6.8±3.6 | 7.4±4.4 | 14 | 20 | 54 | 45 | 3m | Photodynamic therapy |
| Rifaiy et al. 2017 | 38 | 33.6±2.8 | 35.4±2.1 | 38 | 27 | 4.06 | 4.36 | 20 | 18 | - | - | 3m | Photodynamic therapy |
| Karimi et al. 2016 | 10 | - | - | 15 | 15 | - | - | - | - | - | - | 3m | Photodynamic therapy |
| Javed et al. 2017 | 54 | 50.6±0.8 | 52.2±0.5 | 28 | 26 | - | - | 28 | 26 | - | - | 3m | Photodynamic therapy |
| Wang et al. 2019 | 131 | 44.1±9.8 | 42.6±13.0 | 66 | 65 | - | - | 13 | 21 | - | - | 6m | Photodynamic therapy |
| Alqahtani et al. 2019 | 98 | 54.7±3.7 | 54.2±2.2 | 49 | 49 | - | - | 66 | 32 | - | - | 6m | Photodynamic therapy |
| Porras et al. 2002 | 16 | - | - | 16 | 12 | - | - | - | - | - | - | 3m | Chlorhexidine |
| Heitz et al. 2011 | 29 | 57 | 53 | 14 | 15 | - | - | 2 | 2 | 9 | 9 | 3m | Chlorhexidine |
| Levin et al. 2015 | 37 | - | - | 18 | 19 | - | - | - | - | - | - | 3m | Chlorhexidine |
| Menezes et al. 2016 | 37 | 57.4±9.1 | 57.4±13.0 | 61 | 58 | - | - | - | - | - | - | 6m | Chlorhexidine |
| Roos et al. 2017 | 16 | - | - | 16 | 16 | - | - | - | - | - | - | 3m | Chloramine |
| Shibli et al. 2019 | 40 | - | - | 20 | 20 | - | - | - | - | - | - | 12m | Systemic antibiotics |
| Hallstrom et al. 2012 | 43 | 54.6±18.2 | 54.6±19.8 | 22 | 21 | 10.9±4.6 | 10.0±5.2 | - | - | - | - | 6m | Systemic antibiotics |
| Galofre et al. 2018 | 44 | 61.6±12.5 | 58.4±13.3 | 22 | 22 | - | - | - | | - | - | 3m | Probiotic |
| Laleman et al. 2020 | 19 | 64 ± 11 | 69 ± 9 | 9 | 10 | - | - | 0 | 0 | - | - | 6m | Probiotic |

Table 2. Results of the quality assessment of RCTs.

| author, year | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) |
|---|---|---|---|---|---|---|
| Tapia et al. 2019 | Low | High | Low | Low | Low | Low |
| Ji et al. 2012 | Low | Low | Unclear | Unclear | Low | Low |
| Arısan et al. 2015 | Low | Unclear | Low | Low | High | Low |
| Aimetti et al. 2018 | Low | Unclear | Unclear | Unclear | Low | Low |
| Rifaiy et al. 2017 | Low | Unclear | Low | Unclear | Low | Low |
| Karimi et al. 2016 | Low | Low | Low | Low | Low | Low |
| Javed et al. 2017 | Low | Unclear | Unclear | Unclear | Low | Low |
| Wang et al. 2019 | Low | Low | Low | Low | Low | Low |
| Alqahtani et al. 2019 | Low | Unclear | Low | Unclear | Low | Low |
| Heitz et al. 2011 | Low | Low | Low | Low | Low | Low |
| Menezes et al. 2016 | Low | High | Unclear | Unclear | Low | Low |
| Porras et al. 2002 | High | High | High | Unclear | Low | Low |
| Roos et al. 2017 | Low | Low | Unclear | Low | Unclear | Low |
| Levin et al. 2015 | Low | Low | Unclear | Low | High | Low |
| Shibli et al. 2019 | Low | Low | Low | Low | Low | Low |
| Hallstrom et al. 2012 | Low | Low | Low | Low | Low | Low |
| Galofre et al. 2018 | Low | Unclear | Unclear | Low | Low | Low |
| Laleman et al. 2020 | Low | Low | Low | Low | Low | Low |

# Figures

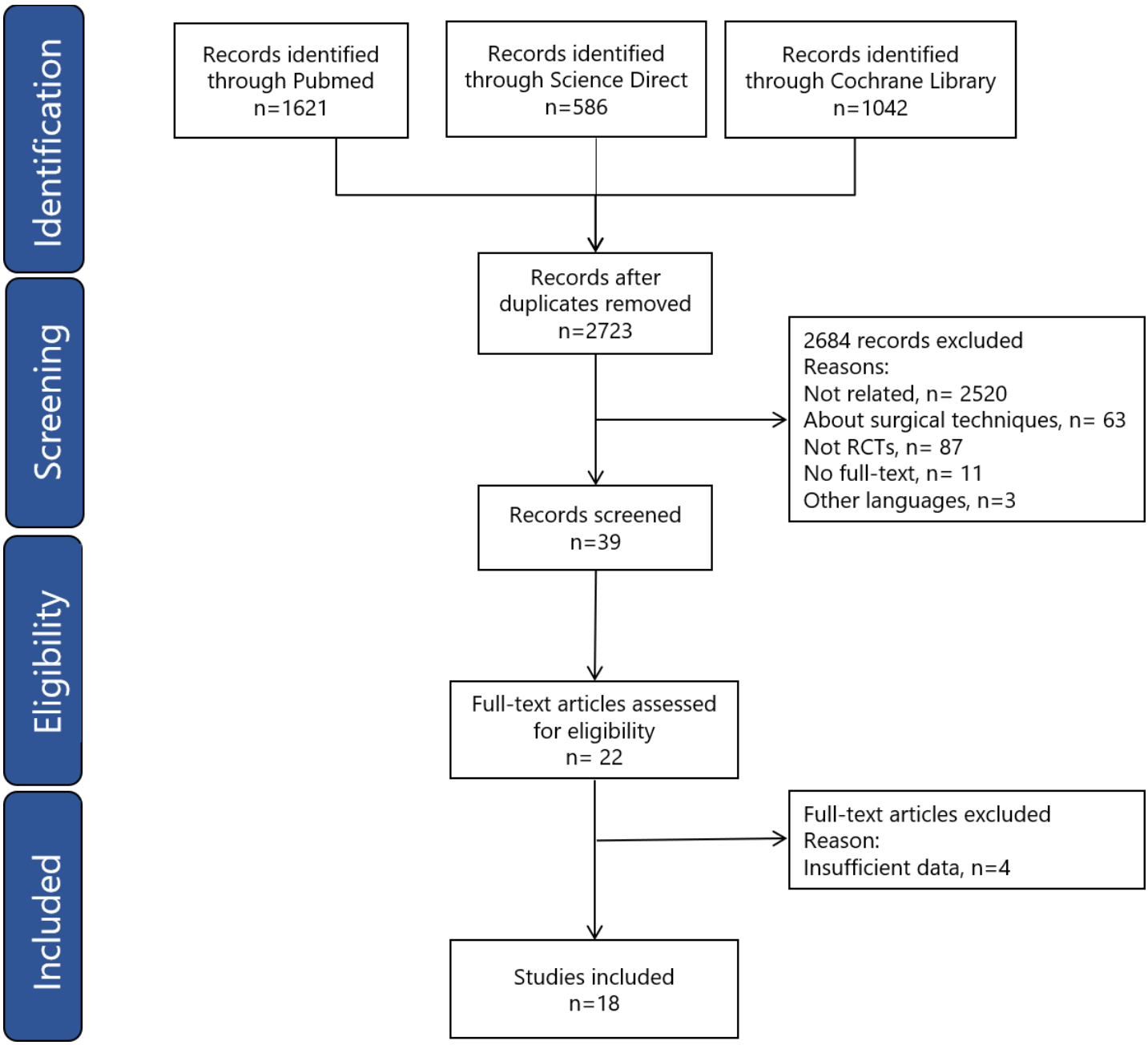
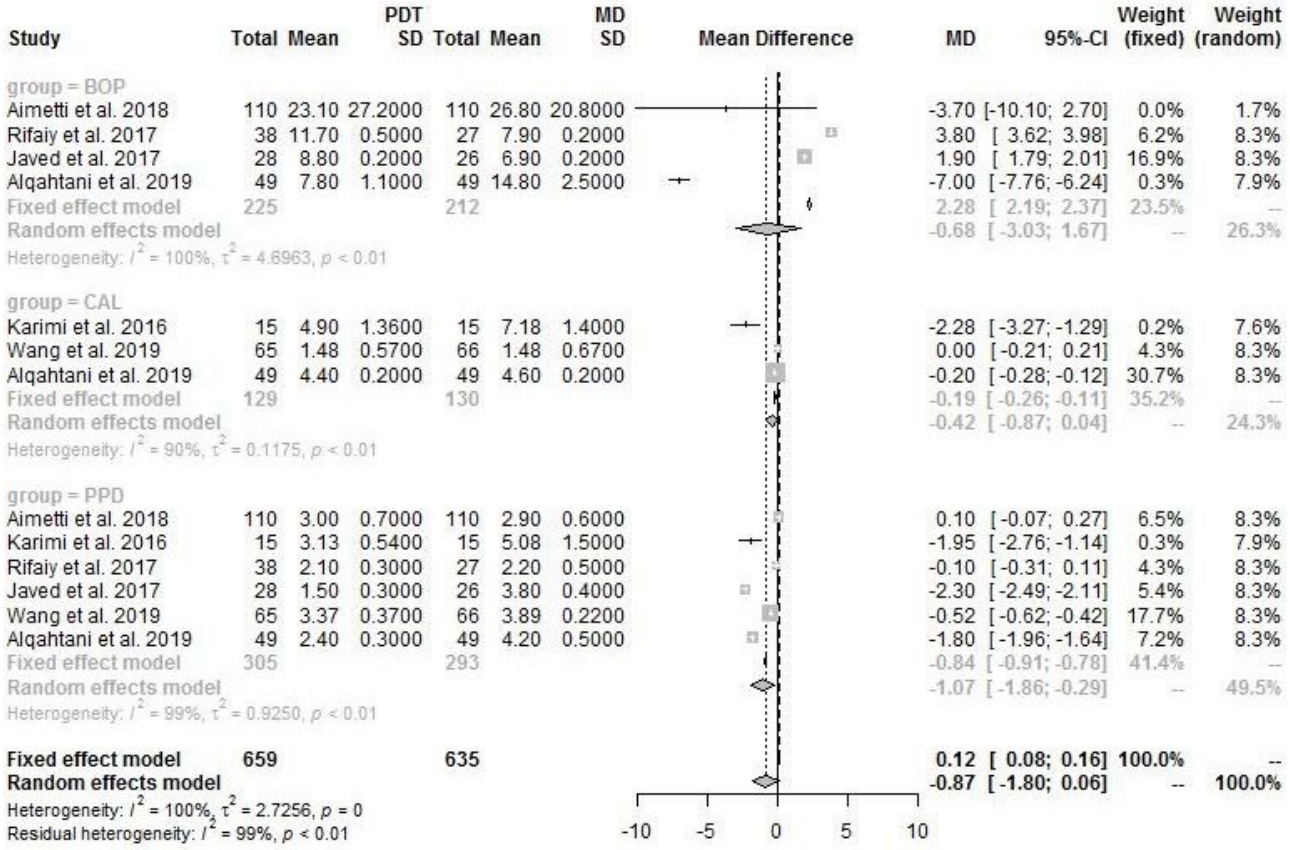


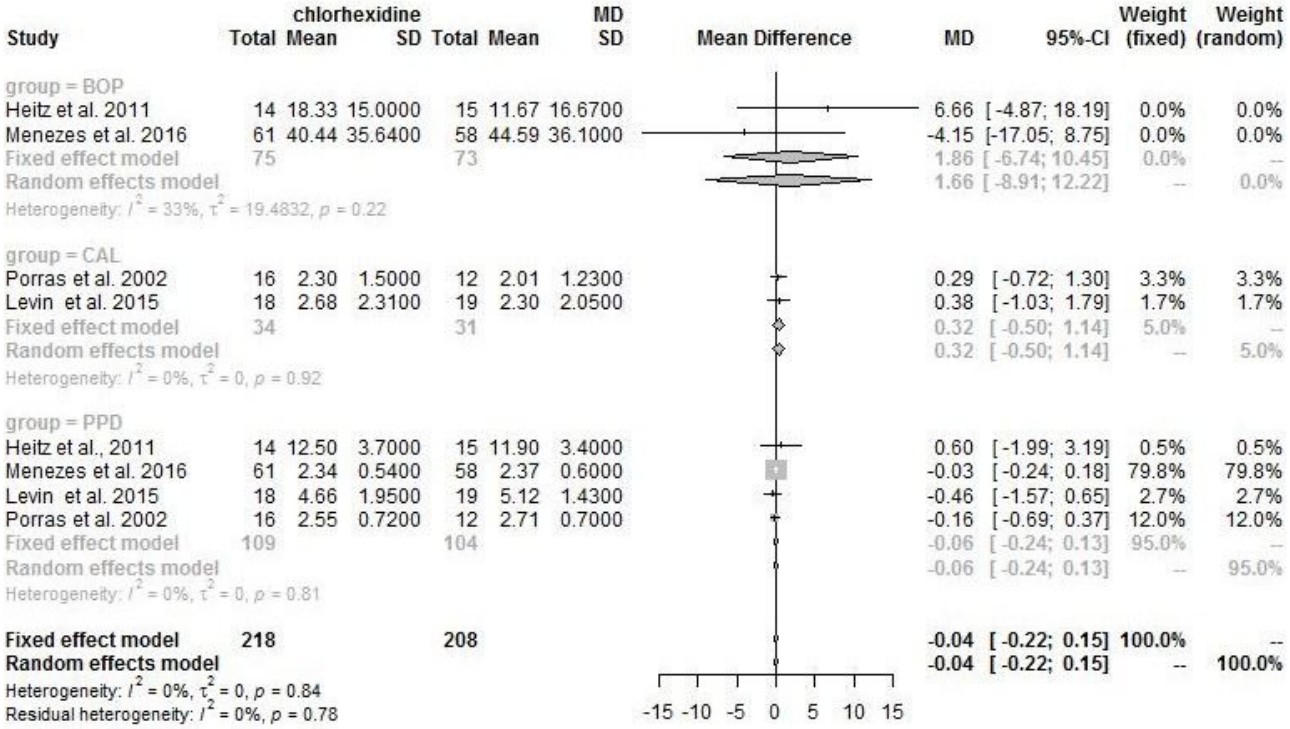

**Figure 1**

Flow chart of manuscripts screened throughout the review process.




## Figure 2

Meta-analysis compares the clinical outcomes of group MD with photodynamic treatment and group MD alone after 3 months follow-up.




## Figure 3

Meta-analysis compares the clinical outcomes of group MD with chlorhexidine treatment and group MD alone after 3 months follow-up.

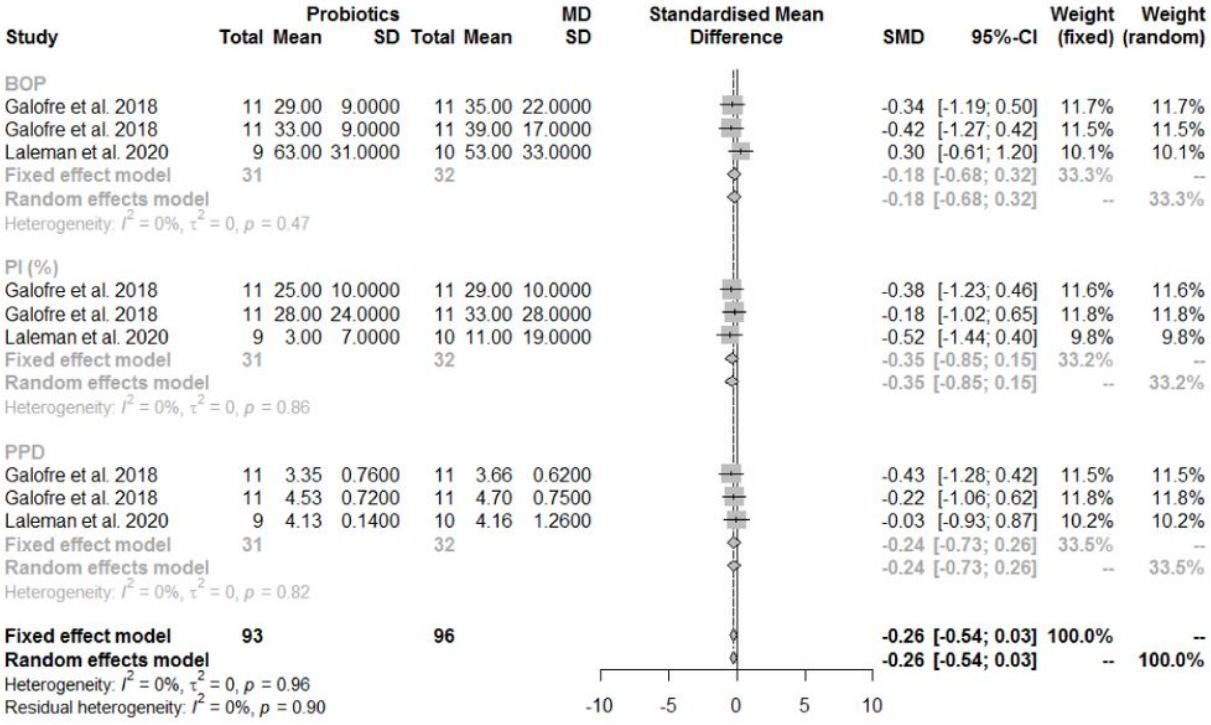


**Figure 4**

Meta-analysis compares the clinical outcomes of group MD with probiotics treatment and group MD alone after 3 months follow-up.

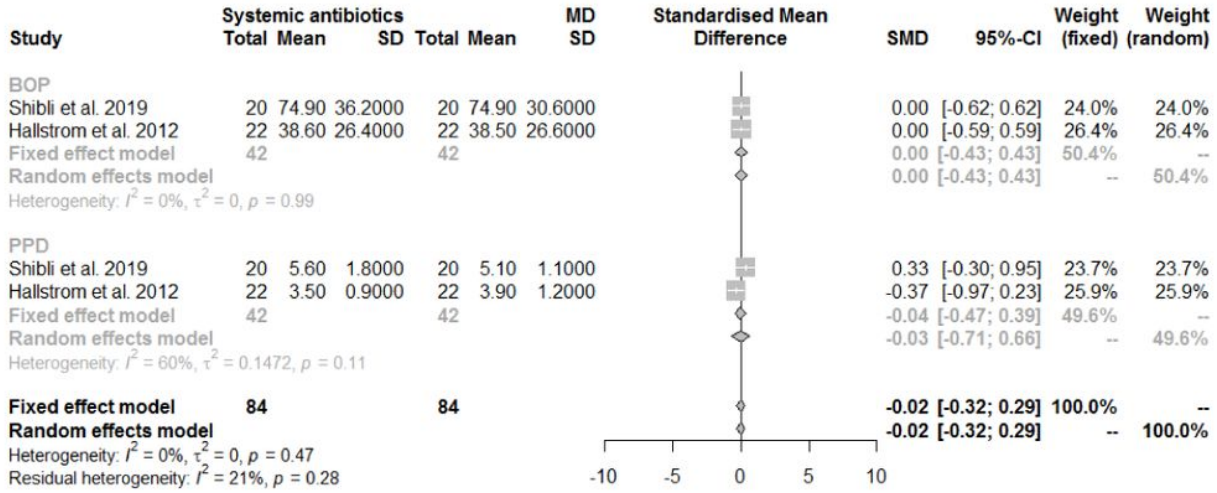



**Figure 5**

Meta-analysis compares the clinical outcomes of group MD with systemic antibiotics treatment and group MD alone after 3 months follow-up.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc