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BEST-EVIDENCE CONSENSUS

# Efficacy of biologics for the treatment of periodontal infrabony defects: An American Academy of Periodontology best evidence systematic review and network meta-analysis

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## Abstract

**Background:** A large variety of biomaterials, biologics and membranes have been utilized in the past 40 years for the regenerative treatment of periodontal infrabony defects. Biologic agents have progressively gained popularity among clinicians and are routinely used for periodontal regeneration. In alignment with the goals of the American Academy of Periodontology (AAP) Best Evidence Consensus (BEC) on the use of biologic mediators in contemporary clinical practice, the aim of this sytematic review was to evaluate the effect of biologic agents, specifically autogenous blood-dervied products (ABPs), enamel matrix derivative (EMD) and recombinant human platelet-derived growth factor-BB (rhPDGF-BB), on the regenerative outcomes of infrabony defects.

**Methods:** A detailed systematic search was conducted to identify eligible randomized control trials (RCTs) reporting the outcomes of periodontal regenerative therapy using biologics for the treatment of infrabony defects. A frequentist mixed-modeling approach to network meta-analysis (NMA), characterized by the assessment of three individual components for the treatment of an infrabony defect (the bone graft material [BG], the biologic agent, the application of a barrier membrane) was performed to evaluate and compare the relative efficacy of the different components, on the outcomes of different therapeutic modalities of periodontal regeneration.

**Results:** A total of 153 eligible RCTs were included, with 150 studies contributing to the NMA. The quantitative analysis showed that the addition of biologic agents to bone graft significantly improves the clinical and radiographic outcomes, as compared to BG and flap procedures alone. Barrier membranes enhanced the regenerative outcomes of BG but did not provide further benefits in combination with biologics. The type of BG (autogenous, allogeneic, xenogeneic or alloplastic) and the biologic agent (EMD, platelet-rich fibrin [PRF], platelet-rich plasma [PRP] or rhPDGF-BB) played a significant role on the final outcomes of infrabony defects. Allogeneic and xenogeneic BGs exhibited statistically significantly superior clinical gain than synthetic and autogenous BGs ($p < 0.05$ in all the

  

comparisons), while rhPDGF-BB and PRF demonstrated significantly higher stability of the gingival margin ($p < 0.01$) and radiographic bone fill/gain ($p < 0.05$), together with greater, although not statistically significant, clinical attachment level gain and pocket depth reduction, than EMD and PRP. Overall, rhPDGF-BB exhibited the largest effect size for most parameters, including clinical attachment level gain, pocket depth reduction, less gingival recession and radiographic linear bone gain. Considering the relatively high number of trials presenting an unclear or high risk of bias, the strength of recommendation supporting the use of PRP was judged weak, while the recommendation for EMD, PRF and rhPDGF-BB was deemed in favor.

**Conclusions:** Biologics enhance the outcomes of periodontal regenerative therapy. Combination therapies involving BGs + biologics or BGs + barrier membrane demonstrated to be superior to monotherapies. The choice of the type of BG and biologic agent seems to have significant impact on the clinical and radiographic outcomes of infrabony defects.

**KEYWORDS**
bone grafts, gingival recession, growth factors, infrabony defects, periodontal regeneration

## 1 | INTRODUCTION

The global prevalence of periodontitis is very high, contributing to the progressive destruction of periodontal tissues which may result in gingival recession, dental hypersensitivity, tooth mobility, and eventually tooth loss.[1–3] Without treatment interventions, incidents of patients' deteriorating quality of life have been reported.[1–3] The ultimate goal of periodontal therapy includes arresting the progression of disease as well as regeneration of the lost tissues such as bone, cementum, and periodontal ligament. Following the first human report demonstrating that periodontal regeneration could be achieved by using Millipore membranes[4] for selective cell exclusion and migration, several techniques involving the application of barrier membranes to treat infrabony defects have been described.[5–9] These barrier membrane approaches – defined as "guided tissue regeneration (GTR)" – typically require more invasive surgical access and flaps for positioning the membrane over the infrabony defect, potentially increasing patient morbidity and the chance of postoperative complications.[8,10–12]

The introduction of biologic agents in recent years has revolutionized the concept and predictability of periodontal regeneration. Novel minimally invasive surgical procedures could be combined with signaling molecules, without necessarily using barrier membranes.[8,11–13] Enamel matrix derivative (EMD), recombinant human platelet-derived growth factor-BB (rhPDGF-BB), fibroblast growth factor-2 (FGF-2), autologous blood-derived products (ABPs), including platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), growth differential factor-5 (GDF-5) and teriparatide are the biologics that have been investigated for the treatment of infrabony defects.[9,14–19] ABPs, such as platelet-rich plasma, plasma rich in growth factors, and platelet-rich fibrin, are generated after the centrifugation of the patient's blood to separate and obtain fractions of whole blood containing a supraphysiologic concentration of some cell types (e.g., platelets) and growth factors.[20,21] ABPs have been investigated as wound healing promoters in diverse clinical applications, including periodontal regeneration.[21,22] EMD was the first biologic agent applied for regenerating the lost periodontium.[20,23,24] Based on the observation that specific enamel matrix proteins are deposited on the developing tooth roots before cementum formation,[25,26] EMD is obtained from the purified fraction of the enamel layer of porcine fetal tooth and, in combination with other natural molecules (mainly amelogenin and enamelin), has been shown to promote proliferation and migration of cells from the periodontal ligament.[27–29] rhPDGF-BB is a potent mitogen that promotes periodontal regeneration by stimulating both chemotaxis and proliferation of periodontal ligament, osteoprogenitor and mesenchymal stem cells.[30] It has been demonstrated that rhPDGF-BB is the strongest isoform to elicit fibroblast's mitogenic and chemotactic response from the periodontal ligament.[31]

In alignment with the purpose of the American Academy of Periodontology (AAP) Best Evidence Consensus (BEC) on the use of biologic mediators in

contemporary clinical practice, the aim of this systematic review is to assess the efficacy of biologics in the treatment of periodontal infrabony defects—defined as vertical bony defects characterized by one-wall, two-wall, three-wall or combined[32,33] defects—by addressing the following focused question: "What is the effect of using biologics (i.e., ABPs, EMD and rhPDGF-BB) on the results of regenerative periodontal therapy of infrabony defects, in terms of clinical and radiographic outcomes, healing response, complications, esthetic outcomes and patient-reported outcome measures (PROMs)?"

## 2 | MATERIALS AND METHODS

### 2.1 | Protocol registration and reporting format

The protocol for the present review was designed according to the Cochrane guidelines[34] and reported with the Preferred Reporting Items for Systematic reviews and Meta–Analysis Extension (PRISMA)[35] – 2020 statement for systematic reviews incorporating network meta-analyses for health care interventions.[36,37] The study protocol was registered and allocated the identification number CRD42022295792 in the PROSPERO database, hosted by the National Institute for Health Research, University of York, Center for Reviews and Dissemination.

### 2.2 | PICOT question

The following Population, Intervention, Comparison, Outcomes, and Time (PICOT) framework[38] was used to guide the inclusion and exclusion of studies for the above-mentioned focused questions:

- Population (P): adult patients (≥ 18 years old) with a history of periodontitis and at least one infrabony defect (≥ 3 mm in depth);
- Intervention (I): periodontal regenerative surgical treatment involving the use of ABPs, EMD, rhPDGF-BB;
- Comparison (C): any comparison among EMD, rhPDGF-BB, and ABPs or between EMD, rhPDGF-BB, or ABPs and conventional approaches (flap alone, bone graft [BG] alone and GTR procedures);
- Outcome (O): Clinical Attachment Level (CAL) gain as the primary outcome. Secondary outcomes included probing depth reduction (PD red), changes in gingival recession (REC), in keratinized tissue width (KT) gain, gingival thickness (GT) gain, bone fill (either radiographically or directly evaluated through surgical re-entry), wound healing outcomes, safety (in terms of complications and adverse reactions), esthetic outcomes and PROMs.
- Time (T): Minimum follow-up of 6 months following surgical intervention.

### 2.3 | Eligible studies

To specifically address the focused question, only randomized controlled clinical trials (RCTs) were included in this systematic review's qualitative and quantitative assessment. RCTs were considered eligible for inclusion if they met the following criteria in at least one study arm: i) Periodontal regenerative surgical therapy of adult patients (≥ 18 years old) presenting infrabony defects (≥ 3 mm in depth); ii) Minimum follow-up of 6 months; iii) Use of a biologic agent (ABPs, EMD or rhPDGF-BB), either as a monotherapy or in combination with BG and/or absorbable barrier membranes (guided tissue regeneration [GTR]); iv) Minimum of 10 participants at the first follow-up (≥ 6 months) for at least one study arm(s) utilizing ABPs, EMD or rhPDGF-BB; v) Eligible therapies included the use of minimally invasive or conventional (open flap debridement) approaches.

Reasons for article exclusion included: i) Treatment of horizontal defects, suprabony defects or endo-perio lesions; ii) Nonsurgical therapy; iii) Less than ten patients at the first follow-up; iv) No use of biologic agents (ABPs, EMD or rhPDGF-BB); v) Multiple combinations of biologic agents (e.g., EMD + ABPs); vi) Biologics combined with GTR techniques using nonabsorbable membranes; vii) Biologic agents combined with stem cells or with laser therapy. RCTs with at least one treatment arm meeting the above-mentioned eligibility criteria were included in the present review. Data from the excluded treatment arm(s) were not considered.

### 2.4 | Outcome measures

Clinical, radiographic imaging, esthetic, safety, and patient-reported outcome measures (PROMs) were assessed as follow:

- Clinical outcomes performed by the investigators including CAL gain, PD red, REC, KT gain or GT gain.
- Radiographic imaging outcomes defined as two dimensional (using periapical radiographs) or three dimensional (using cone-beam computed tomography [CBCT] or computed tomography [CT]) including radiographic bone fill (rBF, measured in percentage) and linear bone gain (rLBG, measured in millimeters).
- Early wound healing outcomes evaluated by the investigators using the early wound-healing index proposed by Wachtel and coworkers[39], evaluation of primary closure, degrees of swelling, or other composite wound healing indices.

- Bone healing outcomes assessed with direct measurements during the surgical re-entry, in terms of vertical defect fill and vertical alveolar crest resorption.
- Esthetic outcomes evaluated through professional esthetic assessments performed by operators either through direct clinical examination or indirectly using standardized intraoral photographs.
- PROMs defined as quality-of-life assessments made by patients regarding different aspects of therapy, such as intrasurgical and postoperative pain/discomfort, painkillers intake, self-reported bleeding and swelling, interference with daily activities, overall satisfaction, esthetic assessment, and occurrence of adverse events using standardized methods of assessment (e.g., visual analog scale [VAS] or questionnaires).
- Safety outcomes defined as observations from the investigators on occurrence of complications and adverse events during the study period.

## 2.5 | Information sources and search strategy

To identify eligible articles, detailed search strategies were modeled for MEDLINE (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases. Searches were conducted to identify papers published up to December 31th, 2021, based on the following comprehensive search strategy: ((("autologous blood-derived products" OR "platelet-rich plasma" OR "platelet-rich fibrin" OR "leukocyte–platelet-rich fibrin" "plasma rich in growth factors" OR "PRP" OR "PRF" OR "L-PRF" OR "PRGF") OR ("platelet-derived growth factor" OR "PDGF")) OR ("enamel matrix protein" OR "EMD")) AND (((((("infrabony defect") OR ("intra bony defect")) OR ("infrabony defect")) OR (infra bony defect)) OR (periodontal regeneration)) OR ("periodontal regenerative"). The search strategy was primarily designed for the MEDLINE database with a string of medical subject headings and free-text terms and then modified appropriately for other databases. No restrictions were set for language. The search results were downloaded to a bibliographic database to facilitate duplicate removal and cross-reference checks.

The reference lists of the retrieved studies for full-text screening and previous reviews in periodontal regeneration were screened. A manual search was also performed in the *Journal of Periodontology, Journal of Clinical Periodontology, Journal of Dental Research, Journal of Periodontal Research, International Journal of Periodontics and Restorative Dentistry, and Clinical Oral Investigations*. Previous systematic reviews in the surgical treatment of infrabony defects were also assessed.[8,15,33,40–48]

## 2.6 | Article selection process

Two independent reviewers (LT and CYC) screened the titles and abstracts (if available) of the entries identified in the literature search in duplicate and independently. Next, the full-text version of all studies that potentially met the eligibility criteria or for which there was insufficient information in the title and abstract to make a decision were obtained. Any article considered potentially relevant by at least one of the reviewers was included in the next screening phase. Subsequently, the full-text publications were also evaluated in duplicate and independently by the same review examiners. Disagreements between the review authors were resolved by open discussion. If no consensus could be reached, a third author (DMK) was consulted. All articles that did not meet the eligibility criteria were excluded, and the reasons for exclusion were noted. Interexaminer agreement following full-text assessment was calculated via kappa statistics. Any missing information that could contribute to this systematic review was requested to the corresponding author(s) via email communication. In the case of multiple publications reporting on the same study or investigating the same cohort at different follow-up intervals (or secondary analysis of the same data), it was decided to pool together all relevant details as a single report with the most comprehensive data for inclusion in the qualitative and quantitative analyses.

## 2.7 | Data extraction

Two examiners (LT and CYC) independently retrieved all relevant information from the included articles using a data extraction sheet specifically designed for this review. Aside from the outcomes of interest (CAL gain, PD red, changes in REC, keratinized tissue with and gingival thickness, rBG, rLBG, early wound healing outcomes, bone healing outcomes, esthetic outcomes, PROMs and safety), the following study characteristics were retrieved: i) Year of publication, study design (split-mouth vs parallel-arm, single vs. multicenter), geographic location, setting (university vs. private practice) and source of funding; ii) Population characteristics, including age and sex of participants, number of participants and treated sites (baseline/follow-up), inclusion of smokers and defect location (maxilla and/or mandible, single and/or multirooted teeth); iii) Characteristics of the infrabony defect, in terms of morphology (remaining walls) and infrabony defect depth (IDD), defined as the vertical distance from the alveolar crest to the deepest location of the osseous defect, assessed either intrasurgically and/or radiographically[49,50]; iv) Type of intervention (flap design); v) Biologic agent and biomaterials utilized; and vi)

Follow-up time points. All values were extracted from the selected publications (mean ± standard deviations [SD]).

## 2.8 | Methodological quality and risk of bias assessment

The assessment of methodological quality and risk of bias (RoB−1) of each included RCT was performed in duplicate, according to the recommended approach by the Cochrane collaboration group[51] (Supplementary Appendix in online *Journal of Periodontology*). Any disagreement was discussed between the same authors. Another author (DMK) was consulted in case no agreement was reached. However, no study was excluded based on the risk of bias within a study.

## 2.9 | Synthesis of quantitative results – network meta-analysis

To assess the relative performance of the available modalities for the treatment of infrabony defects, a frequentist mixed-modeling approach to network meta-analysis (NMA) was adopted.[52,53]

In theory and clinical practice, the treatment of an infrabony defect can be composed of several elements (the BG material, a barrier membrane, and/or a biologic agent) each of which could potentially influence different outcomes of therapy, directly and in combination, and to varying degrees. Therefore, by using the latitude provided by mixed models, these facets were explored through a modeling approach, in which additive and interactive models were considered for each outcome, and the resulting models were compared based on goodness of fit. In an additive model, the effect of BG material (whether autogenous, allogeneic, xenogeneic, synthetic, or none), the biologic agent (ABPs, EMD, rhPDGF-BB, or none) and the membrane (whether used or not), each have a quantified effect that is unrelated to the status of the other two factors. In an interactive model, the effect of each of these three factors may depend on the levels of the other two factors as well.

Similar to previous methodologies applied by our group[52,54,55], study arms were weighted by the treated and analyzed sample size (i.e. the number of defects) and clustered by publication. Relevant baseline demographics and clinical characteristics of the defects and treated population were always accounted for in all models by inclusion of fixed covariates. Random effects were also included in the models to capture unique intercepts for study, study arms, as well as random slopes for study by time, and study arm by time (study arm effects were nested in the corresponding study effect). Correlations with study sponsorship (funding), setting, design (parallel versus split-mouth), and the quality appraisal according to the Cochrane risk-of-bias tool for randomized trials (RoB−1)[56] were also tested, and if needed, controlled for in the models.

The construction of the models, was through testing a series of specifications of random and fixed effects via different model structures, utilizing mainly Akaike Information criterion (AIC) as evidence for the model that best fit the data.[57]

Since nonabsorbable membranes are rarely utilized in contemporary practice for the treatment of infrabony defects, treatment arms which utilized a nonabsorbable membrane (e.g. dPTFE) were not considered. Additionally, due to the wide disparity of data among treatment arms of studies with long-term results, and the potential influence of unmeasured patient- and site-level time-varying characteristics which could particularly affect these specific outcomes, it was planned to only consider data within 5 years of treatment. This was performed for the outcomes of changes in CAL (in mm), PD (in mm), REC (in mm), rBF (percentage of radiographic bone fill compared to initial radiographic defect depth), and rLBG (in mm).

The influence of the specific adopted flap design (e.g., open flap debridement, simplified or modified papilla preservation technique, minimally invasive surgical technique, etc.), as well as information on employing minimally invasive approaches were explored and accounted for by creating categorical and binary variables, respectively, for their effect relative to each outcome.

Interactions between the levels of BG material, the biologic agent, and the application of a barrier membrane were also assessed to identify any synergy between any of the treatment components, such that the effect of any component is highly dependent on the status of the other two components (e.g. if the application of EMD would be improved when mixed with a certain BG material, or when utilized with a barrier membrane).

Transitivity was assessed by exploring the distribution of aggregate baseline variables and study-design information to observe for vast difference, in particular if they could act as effect modifiers or confounders.

The robustness of the results in the final models was tested through a series of sensitivity analyses to observe for any meaningful changes in the estimates of the outcomes. All model assumptions were tested.

And for all outcomes, the reference category for the initial comparisons was set as “None” for the BG type, barrier membrane, and biologic agent and contrasts were recorded. Confidence intervals (CIs) were produced, and a p-value threshold of below 0.05 was set for statistical significance.

The statistical analyses were performed by an author with experience in network meta-analyses and linear mixed models (SB), using a specified software‡ and the following statistical packages lme4[58], lmerTest[59], dplyr[60], and tidyr.[61] The igraph[62] and ggplot2[63] packages were used for producing the geometry of the network plot to visualize the within study contrasts and the existing relationships among treatment arms.

### 2.10 | Evidence quality rating and strength of recommendation

Based on the findings from the NMA and on the available data and results of the individual studies included in the present systematic review, critical assessment of the literature and evidence quality rating or strength of recommendation of biologics for the treatment of infrabony defects were conducted. These recommendations were based on the criteria established by the adapted version of the *American Dental Association (ADA) Clinical Practice Guidelines Handbook*.[64] The quality rating on the available evidence assessing the effect of biologics on the regenerative treatment of infrabony defects was evaluated and presented according to the following criteria: i) clinical indications, ii) therapeutic options, iii) adverse events and complications, iv) net benefit rating (benefit-harm estimation), v) level of certainty and vi) strength of clinical recommendations (Supplementary Tables 1–3 of the Appendix in online *Journal of Periodontology*). The Net benefit rating (benefit-harm estimation) involves the assessment of whether the expected benefits outweigh the potential for harm. The level of certainty describes the extent to which there is confidence in the estimate of the effect of therapy considering the available evidence and it can be classified as high, moderate or low. The strength of clinical recommendation reflects the extent to which it is possible to assume that the treatment recommendation is more beneficial than harmful, based on the best available evidence, and it can be classified as strong, in favor, weak, expert opinion for/supports, expert opinion questions the use, expert opinion against, or against (Supplementary Tables 1–3 of the Appendix in online *Journal of Periodontology*).[64-66]

## 3 | RESULTS

### 3.1 | Search results and study selection

The literature search flow diagram is shown in Figure 1. Following the removal of duplicates, 385 records were identified based on titles and abstracts. A full-text assessment was performed for 182 articles. Based on our predetermined inclusion criteria, 153 RCTs13, 17–19, 39, 49, 50, 67–212 were included in the qualitative analysis and 150 trials in the quantitative analysis. The reason for the exclusion of the other 29 articles is reported in Supplementary Table 4 of the Appendix in the online *Journal of Periodontology*. The interexaminer reliability in the screening and inclusion process, as assessed with Cohen's $\kappa$, corresponded to 0.93 for full text evaluation.

### 3.2 | Characteristics of the included studies

Characteristics of the included studies at baseline are reported in detail in Supplementary Tables 5–8 of the Appendix in the online *Journal of Periodontology*. Out of the 153 included RCTs, 123 were performed in a university setting, 11 in private practice, 12 both in university and private practice, while the remaining 7 trials did not specify the study setting. Most of the included studies were performed in Asia (66) and in Europe (63). Twelve trials were follow-up studies – or reported different outcomes – of the same patient population described in studies already included in the present review.[50,98,99,105,155,175,189–192,194,205] Twenty-five treatment arms from 22 studies [73,79,93,96,102,125,131,136,149,157,160,168,169,171,172,182,184,200–202,208,212] did not meet the inclusion criteria and were not considered for the qualitative and quantitative analysis.

### 3.3 | Risk of bias assessment

Most of the included trials (84) showed unclear risk of bias. Forty-seven RCTs were considered having low risk of bias, while the remaining 22 were assigned a high risk of bias. Lack of information on allocation concealment was the most common risk of bias observed across the studies, followed by risk of bias related to blinding of the outcome assessment and blinding of participants and personnel. The risk of bias assessment is reported in detail in Supplementary Table 9 of the Appendix in the online *Journal of Periodontology*.

### 3.4 | Quantitative analysis and results of the mixed-model network meta-analysis

A total of 319 study arms from 150 eligible RCTs, describing the treatment outcomes of 7007 infrabony defects in 6512 subjects, were included in the NMA. As stated above, study arms reporting data beyond 5 years of treatment[99,191,194] were not included in the analyses, as

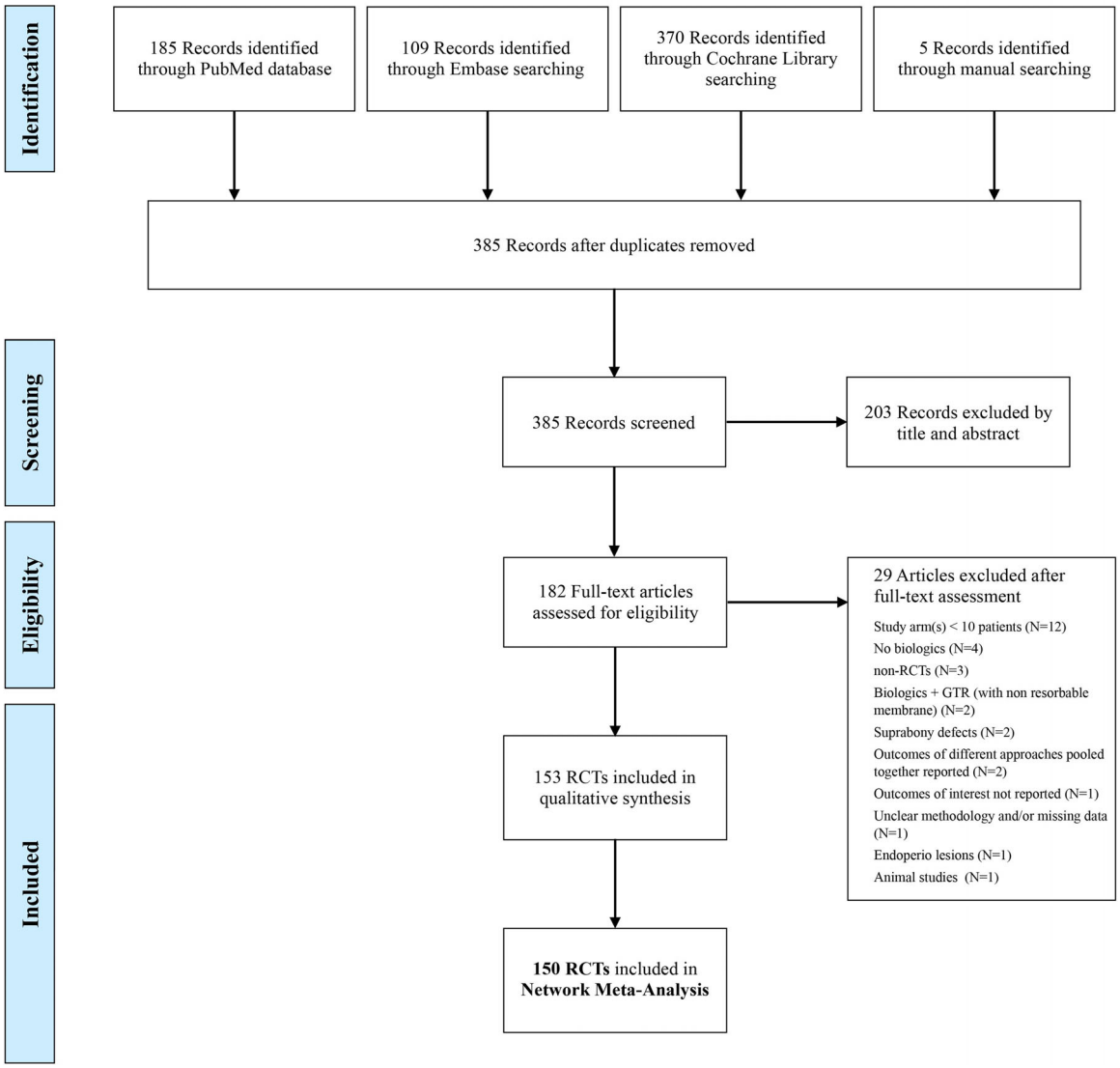


**FIGURE 1** PRISMA flowchart

well as those reporting the use of a nonabsorbable barrier membranes.[93,125,169,200–202,212]

Figure 2 displays the relationships between the existing treatment arms (e.g., xenogeneic BG + EMD) from which the additive model was based upon. One-hundred and twenty-two treatment arms employed EMD.[13,18,19,39,49,50,67,70,73,75–77,79,82,84–86,89,90,93,94,96–99,102,105–109,112–116,121–123,125,126,130,136–138,140–142,146,151,153,156–158,160,167–169,175,177,178,180,182–195,200–202,205–207,209–212], 12 used rhPDGF-BB[17,129,133,139,148,152,155,181], 43 included PRF[19,71,72,74,78,80,81,83,88,91,92,103,110,115,120,131,144,145,149,150,154,162–165,170–174,196–198,203,204], and 31 used PRP.[68,87,95,100,101,117–119,124,127,128,132,134,135,143,147,159,161,166,173,174,179,199] All in all 28 treatment arms also included a barrier membrane.[87,100,112,126,134,143,145,151,162,165,169,176,185,188–191,195] The outcomes of flap procedures alone were reported in 54 study arms.[18,39,49,70,72,74,76,78,80,82,84,86,87,89–92,94,105–109,113,121,128,131,149,152,158,163,164,169–173,175,177,178,190,195,198,200,203–205,210,212] A total of 88 studies utilized BGs[17,19,49,50,67–71,75–78,80,81,83,84,86–88,91,94,95,97–102,104,110–112,114,116–120,122–124,126,127,129,130,132–135,137–148,150,153–157,159,161,164,166,167,170,174,179–181,187,192,193,196,197,199,206,208,209,211], with 7 having utilized an autogenous BG[19,70,110,114,119,150,209], 16 an allograft[67–69,77,78,81,88,116,123,124,135,147,156,157,166,197], 28 a xenograft[49,76,86,87,91,97,98,100–102,111,112,117,126,138,139,141–145,153,174,180,187,196,206,211], and lastly 40 which had reported the application of an alloplastic/synthetic BG.[17,50,71,75,80,83,84,94,95,97,99,104,118,120,122,127,129,130,132–134,137,139,140,146,148,154,155,159,161,164,167,170,179,181,187,192,193,199,208]

Detailed characteristics of the interventions of the included studies are reported in the Supplementary Table 8, while clinical and radiographic outcomes following treatment of infrabony defects are reported in Supplementary Tables 10–22 in the Appendix in the online *Journal of Periodontology*.

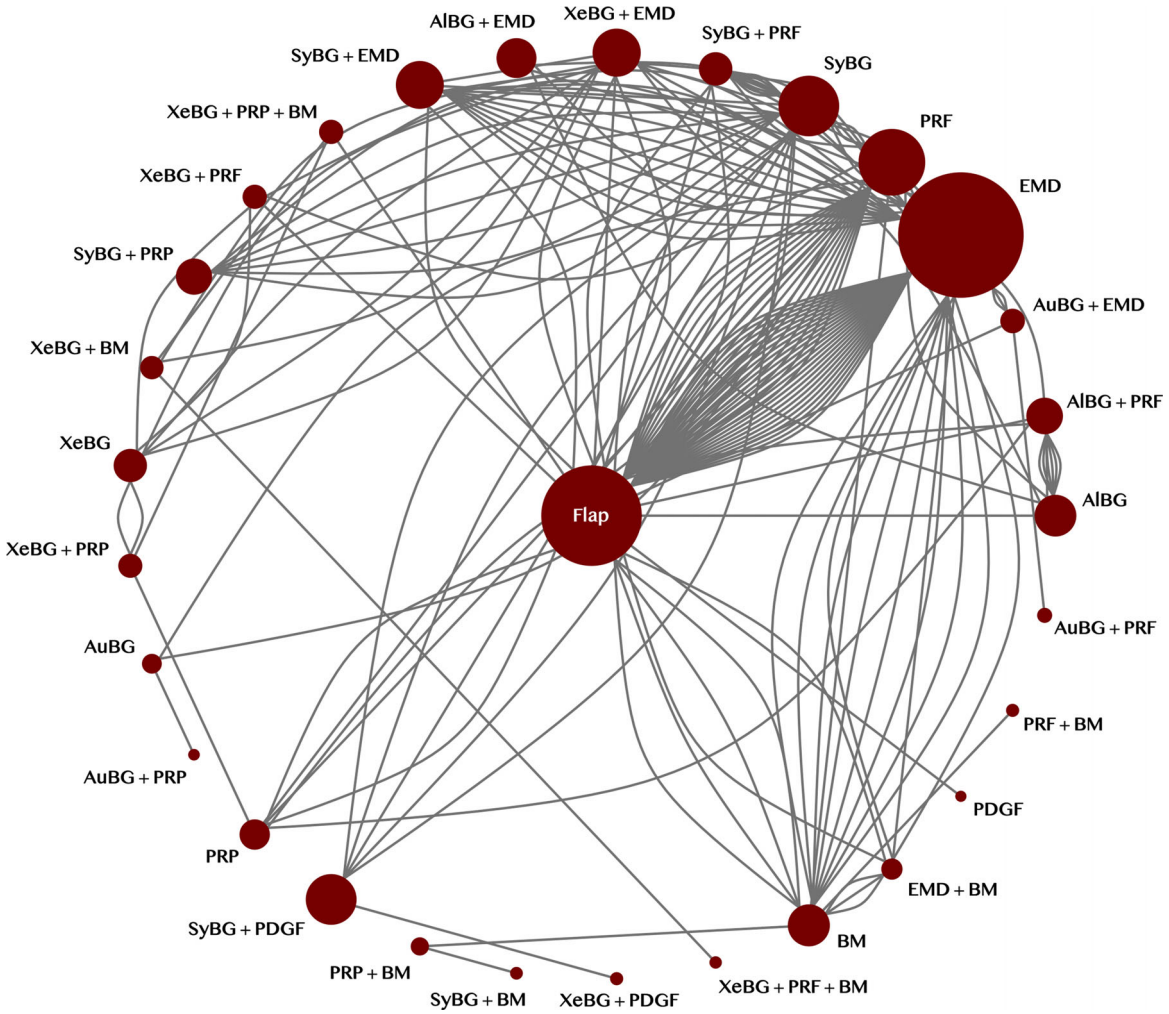


**FIGURE 2** The existing contrasts among studies on the treatment of periodontal infrabony defects, included in the network meta-analysis. Grey solid lines connect treatments of studies that are directly compared head-to-head in at least 1 trial. Note that studies contributing with only one arm are not presented. Distances are for plot clarity. The node size is proportional to the number of treated infrabony defects in that particular treatment arm. AlBG, allogenic bone graft (allograft); AuBG, autogenous bone graft; BM, absorbable barrier membrane; EMD, enamel matrix derivatives; PDGF, platelet-derived growth factor; PRF, platelet–rich fibrin; PRP, platelet–rich plasma; SyBG, synthetic bone graft; XeBG, xenogeneic bone graft; Flap refers to treatment of an infrabony defect utilizing only a debridement process without addition of a bone graft, biologic or barrier membrane

### 3.4.1 | Changes in clinical attachment levels (CAL) (mm)

Based on the model for CAL, it was found that among the BG types, utilization of an allograft (−0.45 (95% CI[−0.89, −0.01]), p = 0.03), and a xenograft (−0.41 (95% CI [−0.77, −0.04]), p = 0.02) would improve the outcomes, whereas the addition of an autogenous (−0.38 (95% CI[−1.04, 0.28]), p = 0.25) and synthetic BG alone (−0.21 (95% [−0.49, 0.07]), p = 0.14) would not lead to significantly enhanced CAL. Additionally, it was shown that overall, the application of an absorbable barrier membrane (−0.79 (95% CI[−1.19, −0.41]), p < 0.01), as well as any biologic agent would improve attachment levels, in an increasing order of effect size, from PRP (−0.58 (95% CI[−0.91, −0.26]), p < 0.01), EMD (−0.61 (95% CI[−0.81, −0.38]), p < 0.01), PRF (−0.82 (95% CI[−1.08, −0.56]), p < 0.01), and rhPDGF-BB with the highest estimate in the model (−1.05 (95% CI[0.48, 1.63]), p < 0.001). Notably, the contrasts between the biologic treatment arms lacked statistical significance.

Furthermore, a negative association with the initial CAL (0.72 (95% CI[0.61, 0.83]), p < 0.001), as well as a positive association with baseline IDD (−0.22 (95% CI[−0.37, −0.08]), p < 0.01) was revealed, whereas no association with time was noted in this model.

Additionally, no interaction between biologic types and BG types was found. Nevertheless, an interaction between membrane (used) with PRF (0.86 (95% CI[0.04, 1.67]),

p = 0.03), as well as between membrane with EMD (0.62 (95% CI[0.015, 1.236]), p = 0.03) was found.

By the logic of this inverse association, the results indicate that membranes are beneficial to the outcomes of CAL in the absence of biologics, however in the presence of biologics the application of a barrier membrane would nullify its effect. This interaction lacked statistical significance for PRP (0.69 (95% CI[−0.63, 2.01]), p = 0.29), and was not found for rhPDGF-BB due to the fact that no treatment arms in the present dataset had utilized rhPDGF-BB with a barrier membrane.

### 3.4.2 | Changes in probing depth (PD) (mm)

Based on the model for this outcome, relative to the choice of BG, it was found that compared to not utilizing a BG (flap alone therapies), the application of an allogeneic (−0.41 (95% CI[−0.73, −0.08]), p = 0.01), autogenous (−0.45 (95% CI[−0.903, −0.007]), p = 0.04), and xenogeneic (−0.51 (95% CI[−0.75, −0.26]), p < 0.01) BG, would lead to improvements, without significant intergroup differences. Regarding the choice of biologic agents, all groups revealed improvement in the outcomes with an increasing order in effect size from PRP (−0.41 (95% CI[−0.66, −0.16]), p < 0.01), EMD (−0.55 (95% CI[−0.71, −0.39]), p < 0.01), PRF (−0.57 (95% CI[−0.76, −0.38]), p < 0.01), and rhPDGF-BB (−0.72 (95% CI[−1.23, −0.21]), p < 0.01).

The application of a barrier membrane was found to improve the overall outcomes of PD, as visible through its main effect in the model (−0.47 (95% CI[−0.74, −0.21]), p < 0.01). Nevertheless, similar to the outcome of CAL, it revealed a statistically significant interaction with EMD (0.66 (95% CI[0.09, 1.24]), p = 0.02), indicating that in the presence of this biologic, the effect of application of a barrier membrane would be nullified.

Lastly, an inverse association with baseline PD (0.34 (95% CI[0.22, 0.45]), p < 0.001) was also noted in this model, as well as a statistically significant, while small in magnitude time effect (0.004 (95% CI[0.0004, 0.0008]), p = 0.02).

### 3.4.3 | Changes in recession depth (REC) (mm)

According to the model, relative to the levels of BG, only utilization of a xenogeneic BG would render significant positive results on the outcome of recession (−0.21 (95% [−0.41, −0.009]), p = 0.03). Regarding biologics, only the groups of PRF (−0.41 (95% CI[−0.59, −0.22]), p < 0.01), and rhPDGF-BB (−0.62 (95% CI[−0.98, −0.25]), p < 0.01) would lead to less recession as a result of therapy compared to a lack of a biologics treatment group. Changing of reference arms also revealed significant differences between EMD and rhPDGF-BB group, in favor of rhPDGF-BB (−0.59 (95% CI[−0.96, −0.22]), p < 0.001), as well as EMD versus PRF, in favor of PRF (−0.39 (95% CI[−0.59, −0.18], p < 0.01)).

Application of a membrane showed no correlation in this model (0.02 (95% CI[−0.19, 0.23]), p = 0.83), while baseline recession (1.04 (95% CI[0.98, 1.11]), p < 0.01) was significantly and inversely associated with the final outcomes (such that the lower/shallower the recession at baseline, the more/deeper the recession depth at the follow-up).

### 3.4.4 | Radiographic bone fill (rBF) (%)

Based on the model, relative to BG materials, only synthetically derived bone substitutes (20.94 (95% CI[10.57, 31.31]), p < 0.01) enhanced this outcome significantly compared to no bone grafting of sites.

Considering biologic agents, all groups showed to significantly enhance the outcomes in an increasing order in effect size from PRP (17.32 (95% CI[6.12, 28.51]), p < 0.01), EMD (19.71 (95% CI[12.78, 26.64]), p < 0.01), rhPDGF-BB (28.78 (95% CI[18.79, 38.75]), p < 0.01), and PRF (29.61 (95% CI[23.28, 35.93]), p < 0.01).

The differences between the biologic agents were statistically significant between EMD and PRF, in favor of PRF (9.89 (95% CI[1.04, 18.75]), p = 0.02), as well EMD versus rhPDGF-BB, in favor of rhPDGF-BB (9.06 (95% CI[1.14, 16.97]), p = 0.02). Relative to PRP, the comparisons of PRP versus PRF (12.28 (95% CI[0.36, 24.21]), p = 0.01), and PRP versus rhPDGF-BB (11.46 (95% CI[0.61, 22.32]), p = 0.02) were also statistically significant (in favor of PRF and rhPDGF-BB, respectively). Nevertheless, the comparison of PRP versus EMD did not reach statistical significance.

The addition of a barrier membrane in this model was also significantly associated with increase in percentage of defect fill (20.81 (95% CI[7.09, 34.52]), p < 0.01), without any interactions. Baseline measures were not revealed to be significantly affecting this outcome.

### 3.4.5 | Radiographic linear bone gain (rLBG) (mm)

It was shown that all BG materials, except for the autogenous group (0.53 (95% CI[−0.28, 1.36]), p = 0.19) would improve this outcome with an increased benefit from synthetic BGs (0.85 (95% CI[0.51, 1.19]), p < 0.01), xenogeneic

BGs (1.15 (95% CI[0.63, 1.67]), p < 0.01), and allogeneic BGs (1.57 (95% CI[1.07, 2.07]), p < 0.01), without intergroup differences.

Regarding biologic agents, it was also found that all biologic agents would improve this outcome, with an increasing benefit from PRP (0.56 (95% CI[0.16, 0.97]), p < 0.01), EMD (0.87 (95% CI[0.59, 1.15]), p < 0.01), PRF (1.28 (95% CI[1.01, 1.55]), p < 0.01), and rhPDGF-BB (1.34 (95% CI[0.88, 1.81]), p < 0.001) with the highest estimate. The statistically significant contrasts between the biologic treatment arms were between PRP and PRF, in favor of PRF (0.71 (95% CI[0.25, 1.17], p = 0.01), as well as PRP versus rhPDGF-BB, in favor of rhPDGF-BB (0.79 (95% CI[0.18, 1.39]), p < 0.01). In addition, between EMD and PRF, in favor of PRF (0.41 (95% CI[0.04, 0.77]), p = 0.02), and between EMD versus rhPDGF-BB, in favor of rhPDGF-BB (0.48 (95% CI[0.15, 0.081]), p = 0.01).

The addition of a barrier membrane was also found to significantly improve the outcomes (1.16 (95% CI[0.48, 1.84]), p < 0.01), without any interaction with a specific treatment arm.

Tables 1 and 2 summarize the main effects of the results of the mixed-model network meta-analysis for the clinical (CAL, PD, REC), and radiographic (rBF, rLBG) outcomes, respectively.

## 3.5 | Qualitative analysis on wound healing outcomes following treatment of infrabony defects

Wound healing outcomes following treatment of infrabony defects were assessed in 13 RCTs[39,49,75,105,113,118,130,138,160,181,205,207,212] (Supplementary Table 23 of the Appendix in online *Journal of Periodontology*). Among them, 8 trials[39,75,105,113,118,130,181,207] utilized the Early wound-healing index (EHI) introduced by Wachtel and coworkers (1-5 degrees, with 1 being the best healing outcome and 5 the worst).[39] Other studies assessed the complete closure of the sites, the degrees of swelling and redness, or the presence of complications.[49,105,113,138,160,205,212] The weighted mean EHI of EMD, flap alone and BG alone at 7 days was 1.78, 1.74 and 2.36, respectively. The weighted mean EHI of EMD, flap alone and BG alone after 14 days was 1.4, 1.17 and 1.99, respectively. Five RCTs comparing EMD with flap alone did not observe statistically significant differences in wound healing outcomes.[39,49,105,113,205] Harnack et al. reported similar healing outcomes for BG with or without PRP.[118] Two trials demonstrated that minimally invasive techniques are associated with lower mean values of EHI, and thus better healing outcomes, as compared to conventional surgical approaches.[181,207]

## 3.6 | Qualitative analysis on bone healing outcomes following treatment of infrabony defects evaluated with surgical re-entry

Fifteen RCTs[86,87,95,109,110,116,118,123,141–144,180,193,206] assessed the hard tissue response following treatment of infrabony defects with a surgical re-entry (Supplementary Tables 24 and 25 of the Appendix in online *Journal of Periodontology*). The weighted mean defect fill for BG alone and flap alone were 2.61 mm and 1.42 mm, respectively, while their weighted mean alveolar crest resorption was 0.36 mm and 0.97 mm, respectively.

The weighted mean defect fill following treatment of infrabony defects with ABPs, ABPs + BG and ABPs + GTR was 2.28 mm, 3.37 mm and 5.05 mm, respectively. The weighted mean alveolar crest resorption at the re-entry following ABPs, ABPs + BG and ABPs + GTR was 1.06 mm, 0.76 mm and 0.94 mm, respectively.

Two trials directly comparing ABP + BG vs BG alone failed to find statistically significant difference for mean defect fill and mean alveolar crest resorption.[95,110]

EMD as a monotherapy showed a weighted mean defect fill and alveolar crest resorption of 2.98 mm and 0.61 mm, respectively, while EMD + BG obtained a weighted mean defect fill and alveolar crest resorption of 3.37 mm and 0.29 mm, respectively. Three RCTs[116,141,206] evaluated the hard tissue outcomes of EMD + BG vs EMD alone with a surgical re-entry. In all of these trials, a statistically significant higher defect fill was observed for the sites treated with EMD + BG compared to EMD only treated sites.[116,141,206] On the other hand, 3 RCTs with surgical re-entry demonstrated that the addition of EMD to BG did not result in a statistically significant changes in terms of defect fill and alveolar crest resorption, as compared to BG alone.[123,142,180]

## 3.7 | Qualitative analysis on PROMs following treatment of infrabony defects

Ten RCTs[49,75,106,113,130,138,160,181,205,212] reported PROMs following treatment of infrabony defects. The weighted postoperative pain following EMD and EMD + BG, evaluated with a 0–10 visual analog scale (VAS), was 2.21 and 2.17, respectively. The weighted VAS indicating postoperative pain following flap alone was 2.49. Only one study[138] described the postoperative morbidity for BG alone using a VAS. The authors observed a statistically significant lower morbidity for EMD + BG compared to BG alone (2.9 vs 4.1).[138] Other studies did not observe statistically significant differences among the treatment groups in terms of painkiller intake. Other PROMs evaluated following treatment of infrabony defects included self-reported

**TABLE 1** Summary of the fixed-effect parameters of the mixed-model network meta-analysis for the clinical outcomes of regenerative therapy for infrabony defects

| | Outcome | | | | | |
|---|---|---|---|---|---|---|
| | CAL change | | PD change | | REC change | |
| | Estimate (mm) | 95% CI [LB, UB], p value | Estimate (mm) | 95% CI [LB, UB], p value | Estimate (mm) | 95% CI [LB, UB], p value |
| Intercept | −0.303 | [−1.21, 0.60], 0.503 | 1.74 | [0.87, 2.61], < 0.01 | 0.75 | [0.58, 0.92], < 0.001 |
| Bone graft Allogenic | −0.45 | [−0.89, −0.01], 0.03 | −0.41 | [−0.73, −0.08], 0.01 | −0.105 | [−0.35, 0.14], 0.4 |
| Bone graft Autogenous | −0.38 | [−1.04, 0.28], 0.25 | −0.45 | [−0.903, −0.007], 0.04 | −0.03 | [−0.45, 0.38], 0.87 |
| Bone graft Synthetic | −0.21 | [−0.49, 0.07], 0.14 | −0.16 | [−0.36, 0.03], 0.11 | 0.06 | [−0.11, 0.24], 0.44 |
| Bone graft Xenogeneic | −0.41 | [−0.77, −0.04], 0.02 | −0.51 | [−0.75, −0.26], < 0.01 | −0.21 | [−0.41, −0.009], 0.03 |
| Barrier membrane (used) | −0.79 | [−1.19, −0.41], < 0.01 | −0.47 | [−0.74, −0.21], < 0.01 | 0.02 | [−0.19, 0.23], 0.83 |
| Biologic EMD | −0.61 | [−0.81, −0.38], < 0.01 | −0.55 | [−0.71, −0.39], < 0.01 | −0.02 | [−0.14, 0.10], 0.75 |
| Biologic PDGF | −1.05 | [0.48, 1.63], < 0.001 | −0.72 | [−1.23, −0.21], < 0.01 | −0.62 | [−0.98, −0.25], < 0.01 |
| Biologic PRF | −0.82 | [−1.08, −0.56], < 0.01 | −0.57 | [−0.76, −0.38], < 0.01 | −0.41 | [−0.59, −0.22], < 0.01 |
| Biologic PRP | −0.58 | [−0.91, −0.26], < 0.01 | −0.41 | [−0.66, −0.16], < 0.01 | −0.19 | [−0.44, 0.04], 0.102 |
| Biologic EMD by membrane (yes) interaction | 0.62 | [0.01, 1.23], 0.03 | 0.66 | [0.09, 1.24], 0.02 | – | – |
| Biologic PRF by membrane (yes) interaction | 0.86 | [0.04, 1.67], 0.03 | 0.13 | [−0.62, 0.89], 0.71 | – | – |
| Biologic PRP by membrane (yes) interaction | 0.69 | [0.63, 2.01], 0.29 | 0.16 | [−0.46, 0.79], 0.6 | – | – |

*Note*: that results of the fixed-effect parameters are expressed according to each parameter as indicated in the estimate parenthesis.
The shown intercept for each outcome refers to the estimated treatment effect from the model, for a periodontal infrabony defect merely with surgical debridement alone, without the addition of a biologic factor, a bone grafting material, or a bioabsorbable barrier membrane.
Due to the additive nature of this model, to estimate the effect of a treatment (any combination of a biomaterial, membrane, or biologic agent), the corresponding treatment effects are to be added accordingly, the summation of which constitutes the overall effect from that therapy, when added to the intercept (as the starting point).
**Legend**. EMD, enamel matrix derivatives; PDGF, recombinant human platelet-derived growth factor-BB; PRF, platelet–rich fibrin; PRP, platelet–rich plasma. CI, confidence intervals; LB, lower bound, UB, upper bound.

intraoperative hardship of the surgical procedure, postoperative bleeding, swelling, root hypersensitivity, edema, hematoma, fever, interference with daily activities, satisfaction, esthetic assessment and willingness to retreat (Supplementary Table 26 of the Appendix in online *Journal of Periodontology*). A multicenter RCT did not detect any benefits from adding EMD to open flap debridement, compared to flap alone, in terms of PROMs (intrasurgical pain, hardship of the procedure, postoperative pain, painkiller intake, duration of pain and interference with daily activities)[205], while other studies showed that EMD may be able to reduce postsurgical bleeding and the duration of pain and swelling.[75,106,138,212]

## 3.8 | Outcomes not explored

Quantitative or qualitative assessment of KT and GT changes, as well as professional esthetic outcomes and complications could not be performed due to the lack of data among the included studies. Five studies reported the radiographic outcomes using CBCTs or CT.[83,115,135,164,174] Due to the few studies reporting this outcome and due to the heterogeneity in the outcome assessment, this aspect was not explored in the quantitative analysis. The five RCTs assessing radiographic outcomes with CBCT/CT investigated the use of ABPs for the treatment of infrabony defects[83,115,135,164,174], with the study of Gupta et al. assessing the outcomes of both PRF and EMD.[115] One study obtained higher percentage of bone fill for ABP + BG over BG alone[83], while another trial reported that ABP + BG obtained greater bone fill than ABP alone.[174] On the other hand, two studies did not find significant differences in terms of radiographic defect resolution between ABP + BG and BG alone.[135,164] When comparing EMD to PRF, one trial observed no significant differences between the two groups for mean defect resolution and changes in defect width and angle.[115] However, EMD obtained a

**TABLE 2** Results of the fixed-effect parameters of the mixed-model network meta-analysis for the radiographic outcomes of regenerative therapy for infrabony defects

| | Outcome | | | |
|---|---|---|---|---|
| | Radiographic bone fill (rBF) | | Radiographic linear bone gain (rLBG) | |
| | Estimate (%) | 95% CI [LB, UB], p value | Estimate (mm) | 95% CI [LB, UB], p value |
| Intercept | 2.32 | [−23.14, 27.81], 0.85 | 0.76 | [0.46, 1.06], < 0.01 |
| Bone graft Allogenic | 14.69 | [−0.68, 30.07], 0.07 | 1.57 | [1.07, 2.07], < 0.01 |
| Bone graft Autogenous | 9.54 | [−21.27, 40.35], 0.53 | 0.53 | [−0.28, 1.36], 0.19 |
| Bone graft Synthetic | 20.94 | [10.57, 31.31], < 0.01 | 0.85 | [0.51, 1.19], < 0.01 |
| Bone graft Xenogeneic | 7.39 | [−11.70, 26.48], 0.44 | 1.15 | [0.63, 1.67], < 0.01 |
| Barrier membrane (used) | 20.81 | [7.09, 34.52], < 0.01 | 1.16 | [0.48, 1.84], < 0.01 |
| Biologic EMD | 19.71 | [12.78, 26.64], < 0.01 | 0.87 | [0.59, 1.15], < 0.01 |
| Biologic PDGF | 28.78 | [18.79, 38.75], < 0.01 | 1.34 | [0.88, 1.81], < 0.001 |
| Biologic PRF | 29.61 | [23.28, 35.93], < 0.01 | 1.28 | [1.01, 1.55], < 0.01 |
| Biologic PRP | 17.32 | [6.12, 28.51], < 0.01 | 0.56 | [0.16, 0.97], < 0.01 |

*Note*: that results of the fixed-effect parameters are expressed according to each parameter as indicated in the estimate parenthesis. The shown intercept for each outcome refers to the estimated treatment effect from the model, for a periodontal infrabony defect merely with surgical debridement alone, without the addition of a biologic factor, a bone grafting material, or a bioabsorbable barrier membrane. Due to the additive nature of this model, to estimate the effect of a treatment (any combination of a biomaterial, membrane, or biologic agent), the corresponding treatment effects are to be added accordingly, the summation of which constitutes the overall effect from that therapy, when added to the intercept (as the starting point).

**Legend**. EMD, enamel matrix derivatives; PDGF, recombinant human platelet-derived growth factor-BB; PRF, platelet–rich fibrin; PRP, platelet–rich plasma. CI, confidence intervals; LB, lower bound, UB, upper bound.

**TABLE 3** Quality of evidence rating for the effect of biologics on the treatment outcomes of infrabony defects from the included trials

| | Autologous blood-derivative products (ABPs) | | | |
|---|---|---|---|---|
| Criterion | PRP | PRF | Enamel matrix derivatives (EMD) | Recombinant human platelet-derived growth factor-BB (rhPDGF) |
| Adverse events and complications | No | No | No | No |
| Net benefit rating (benefit-harm estimation) | Clinical benefits outweigh potential harms | Clinical benefits outweigh potential harms | Clinical benefits outweigh potential harms | Clinical benefits outweigh potential harms |
| Level of certainty | Low to moderate | Moderate | Moderate | Moderate |
| Strength of recommendation | Weak | In favor | In favor | In favor |

significantly greater percentage of defect resolution than PRF.[115]

## 3.9 | Evidence quality rating

Table 3 depicts the adverse events, net benefit rating, level of certainty and strength of recommendation for the use of biologics for the treatment of infrabony defects, based on the results from the NMA and on the outcomes reported in the individual studies. Although some degrees of discomfort and swelling have been described following the use of biologics, no serious or adverse reactions were specifically correlated to ABPs, EMD or rhPDGF-BB. The use of biologic agents, either as a monotherapy or in combination with other biomaterials, can be considered a safe treatment approach for the treatment of infrabony defects. For all investigated biologics, it can also be concluded that the clinical benefits overweight the potential harms. Based on the predetermined criteria recommended for rating the level of certainty, PRP was categorized as low level of certainty due to the relatively high number of studies with high risk of publication bias. On the other hand, EMD, PRF and rhPDGF-BB were considered to be supported by a moderate level of certainty, due to the presence of some studies with high risk of bias or inconsistency of findings across individual studies.

The strength of recommendation supporting the use of PRP for the treatment of periodontal infrabony defects was considered weak, while the strength of recommendation for EMD, PRF and rhPDGF-BB was deemed in favor.

## 4 | DISCUSSION

Currently, although biologics are commonly utilized for periodontal regeneration, evidence supporting their application as a monotherapy or in combination with BGs or barrier membranes for the treatment of infrabony defects is equivocal and inconclusive. The purpose of the present AAP best evidence review was to gather all the existing evidence in properly conducted RCTs on the effect of ABPs, EMD and rhPDGF-BB on the outcomes of periodontal infrabony defects as compared to therapies not involving the use of such products.

### 4.1 | Main findings

The utilization of a mixed model for conducting a NMA allowed to analyze a large number of eligible RCTs. Through this approach in the current study, the authors contrasted and, in essence, separated and isolated the specific components of the utilized treatments among studies, through additive and interactive models, to explore the relative impact of the different BGs, biologics and the application of a barrier membrane on different therapeutic outcomes. This also allowed for obtaining direct and indirect comparisons among the stated treatment constituents, together, and in separation, all of which are vital for an evidence-based quality synthesis with the ultimate goal of improving daily clinical decision-making and patient-care.[52,54,213–215]

Overall, our findings revealed that the addition of biologic agents to BG materials significantly enhances the clinical (CAL gain, PD red, REC change) and radiographic (rBF and rLBG) outcomes of periodontal regeneration as compared to BGs alone and flap procedures. Furthermore, the models did not find any interaction between the levels of biologics and bone graft types.

Nevertheless, the authors noted an interaction between the application of a barrier membrane and biologic agents. Despite the overall positive association of using a membrane with achieving improved outcomes (as the main effect) the negative association in the interaction term implies that the added benefit of using a barrier membrane (for example with a BG) in the presence of biologics would be nullified, thus barrier membranes being beneficial only in the absence of biologic agents.

This finding supports the notion that biologic agents can prevent the apical migration of the epithelium in the periodontal defects.[216–219] It can also be assumed that biologic agents may have higher angiogenic and wound healing capacities when applied without barrier membranes that could otherwise limit and jeopardize the blood supply and chemotaxis of key cells for periodontal regeneration.[17,155,165,220] In an animal study, Simion and coworkers compared the regenerative capacities of xenograft alone, xenograft + rhPDGF-BB and xenograft + rhPDGF-BB + barrier membrane.[219] They reported that the largest amount of newly formed bone was observed at sites treated with xenograft + rhPDGF-BB, while the addition of a barrier membrane seemed to negatively affect the regenerative outcomes of the growth BG soaked with the growth factor, leading the authors to highlight the key role of the periosteum as a source of osteoprogenitor cells in growth factor-mediate regenerative therapies.[219]

Based on our findings, clinicians should be aware that combination therapies involving BG + biologics/barrier membrane should be preferred over monotherapies for the treatment of infrabony defects and also that adding a barrier membrane to a combination therapy already involving BG and biologics is not beneficial. Similarly, when performing GTR procedures, involving a BG and a barrier membrane, the addition of biologics seems not to improve the clinical outcomes.

Nevertheless, the final decision should also take into consideration other factors, including the morphology of the defect.[33] In particular, the addition of barrier membrane may be beneficial in large and noncontained defects, to keep the BG in place and prevent dislodging when suturing and in the early stages of healing.

Other clinical dilemmas not previously addressed in the literature were related to the choice of BG and the biologic agent for periodontal regeneration. Bearing in mind that regulation policies have limited head-to-head comparisons in clinical trials between different biomaterials and biologics in certain countries, the present study demonstrated that the type of BG affects the outcomes of infrabony defects, with allograft and xenograft showing the greatest clinical results, compared to synthetic and autogenous BGs and flap alone. Interestingly, xenograft was the only bone scaffold able to significantly improve the stability of the gingival margin following periodontal regeneration. However, it is reasonable to assume that other factors, including experience and skill of the clinician, surgical technique, KT and GT, play even a more crucial role on the position and stability of the gingival margin.[8]

Another interesting finding from the present analysis was the comparison among different biologic agents, that was performed through multiple direct and indirect comparisons from the NMA models. These results have the potential of guiding clinicians in their decision making process, as the use of biologics has progressively gained popularity in periodontal regeneration, however with little evidence supporting the superiority of one agent versus the other. In particular, PRF has been introduced as a second generation of platelet concentrates, claiming that the different processing method could provide superior outcomes compared to PRP.[20,43] This study found that PRF obtained consistently superior regenerative outcomes than PRP. While the differences in CAL gain and PD red were not statistically significant, PRF outperformed PRP in terms of REC, rBF and rLBG. It has been suggested that one of the main advantages of PRF is the formation of a fibrin-dense clot contributing to extended release of growth factors over time, as compared to PRP where the addition of anticoagulants may interfere with the functions of platelets.[43,221–223] On the other hand, EMD and rhPDGF-BB have been proved to promote periodontal regeneration since the mid 1990s. Results from the present NMA revealed that both EMD and rhPDGF-BB significantly improved the outcomes of periodontal regenerative therapy in infrabony defects and that their use in combination with BGs is justified. Interestingly, rhPDGF-BB showed a superior treatment effect than EMD, which was not statistically significant for CAL gain and PD red, but it was statistically significant higher for REC, rBF and rLBG. Several reasons may explain these findings. Overall, from these multiple comparisons among biologics, it can be concluded that while their use was shown to be consistently beneficial for the treatment of infrabony defects, it seems that rhPDGF-BB and, to a lesser extent, PRF resulted in the highest improvement of the clinical and radiographic outcomes.

It has also to be mentioned that the primary goal of the treatment of infrabony defects has progressively evolved from the regeneration of the defect, that was often demonstrated with surgical re-entry, to probing depth reduction and CAL gain.[8] Our results demonstrated that rhPDGF-BB and PRF were the only biologic therapies with significant beneficial effects on REC, which may be due to their enhanced angiogenic properties.[20,224–228] On the other hand, adding barrier membranes was found to be ineffective for REC. In addition, it is important to mention that baseline recession depth was significantly and inversely associated with the final position of the gingival margin following the treatment of infrabony defects. In other words, the lower the baseline REC, the deeper the final REC should be expected upon tissue maturation. This aspect is particularly crucial nowadays, with overall increased patient demands, at the point that even a minimal recession following periodontal regenerative therapy could be perceived as a treatment failure. Combination of xenogeneic BG and rhPDGF-BB or PRF showed the higher probability of maintaining the stability of the gingival margin following the treatment of infrabony defects.

## 4.2 | Agreements and disagreements with previous reviews

To the best of our knowledge, the present study is the first systematic review evaluating and statistically comparing the outcomes of ABPs, EMD, rhPDGF-BB and traditional approaches for the treatment of periodontal infrabony defects. The authors believe that the findings from this study can positively contribute to the literature and to clinical decision making.

The 2015 AAP Regeneration Workshop has previously addressed the efficacy of different approaches for regenerating periodontal infrabony defects.[16,229] The conclusions from this proceeding were based on a systematic review that qualitatively appraised the available literature.[16] EMD and rhPDGF-BB were shown to be effective treatment modalities for the treatment of infrabony defects with comparable outcomes to GTR (with allogeneic BG) and superior results than flap procedures alone.[16] Our findings further confirmed the effectiveness of EMD and rhPDGF-BB, and their overall superiority compared to flap procedures. The present study also provides evidence supporting the use of ABPs for infrabony defects. The additive and interactive NMA model has allowed us to statistically explore and compare different interventions and combination therapies, from which it could be observed that biologics significantly improve the regenerative clinical and radiographic outcomes of BG alone, and that GTR procedures enhanced the results of BG materials but not those derived from the use of biologics. Although biologics showed overall higher estimates than GTR, the present findings corroborate that these two approaches can be considered comparable for CAL gain, PD red and radiographic bone gain. Nevertheless, rhPDGF-BB and PRF proved to be superior to GTR in promoting stability or minimal change in gingival recession following periodontal regeneration.

While a systematic review and pairwise meta-analysis failed to support additional benefits of EMD as an adjunct to BG for the treatment of infrabony defects,[230] our findings consistently showed that biologics enhanced the clinical and radiographic outcomes of BG materials. This discrepancy with our results was probably due to the fact that the conclusions of the previous review were based on 5 RCTs that were compared using a traditional

pairwise meta-analysis, that did not take into account for effect modifiers, such as type of BGs. Choosing this traditional meta-analysis approach has several disadvantages, such as limiting tremendously the number of eligible RCTs to include in the analysis.

A series of NMAs has been performed by the same group on the treatment of infrabony defects, showing the potential of this tool in comparing multiple treatments.[47,231,232] In line with our findings, the authors concluded that combination therapies provided superior regenerative outcomes compared to monotherapies and flap procedures alone. Nevertheless, using EMD as the only biologic agent and not incorporating in the NMA model possible effects modifiers, such as study funding, risk of bias, depth of infrabony defect, etc. may limit the generalizability of the findings from these studies.

### 4.3 | Limitations

Regarding the limitations of the present study are that few RCTs reported data on wound healing outcomes, complications, changes in gingival phenotype (KT and GT) and PROMs. Qualitative analysis did not highlight substantial benefits of EMD and ABPs in improving early wound healing outcomes or PROMs. Nevertheless, more clinical trials incorporating the evaluation of early wound healing and patient questionnaires are needed to explore these aspects. In addition, it would have been beneficial to analyze individual patient-level data on the morphology of the infrabony defects observed during the surgical procedure. Unfortunately, this information was rarely reported in the included trials and could not be taken into account in the present analysis, except for the depth of the infrabony defect, which was found to play a significant role on the amount of CAL gain. In line with a recent review by Nibali and coworkers[33], the authors of the present study speculate that the morphology of the infrabony defect, in terms of residual walls and wall angles, is a parameter potentially affecting the regenerative outcomes of infrabony defects. It should be highlighted that many included trials were assigned a high or unclear risk of bias, as pointed out in previous reviews.[44,45,233] Therefore, although the results from the present NMA showed a consistent and robust positive effect of biologics on the treatment outcomes of infrabony defects, the evidence supporting the use of biologics and the strength of recommendation were defined in favor of PRF, EMD and rhPDGF-BB, and weak for PRP, due to the risk of bias observed across the studies. Lastly, it has to be mentioned that there are other biologics, including, but not limited to, alternative ABPs, hyaluronic acid and FGF-2, that were not addressed in the present review due to limited available evidence or use in contemporary clinical practice. Future studies are needed to better assess their efficacy in periodontal regeneration of infrabony defects.

## 5 | CONCLUSIONS

Based on the current available evidence, and within the limitations of this study, the following conclusions can be drawn:

1. Biologic agents, including ABPs, EMD and rhPDGF-BB, significantly enhance the clinical and radiographic outcomes of BGs in the treatment of infrabony defects.
2. Combination therapies involving BGs, either with a biologic or a barrier membrane, are the most effective strategies for the treatment of infrabony defects.
3. rhPDGF-BB and PRF were associated with higher clinical and radiographic regenerative outcomes than EMD and PRP.
4. Allogeneic and xenogeneic BGs were associated with greater benefits regarding clinical outcomes than autogenous and synthetic BGs.
5. Xenogeneic BG + rhPDGF-BB or PRF was the best combination therapy for maintaining the stability of the gingival margin following periodontal regeneration of infrabony defects.

### 5.1 | Implications for clinical practice (clinical recommendation)

Based on the results of the present study, clinicians are advised that combination therapies using a BG as a scaffold and biologics (ABPs, EMD and rhPDGF-BB) or a barrier membrane provide superior outcomes than BG and flap procedures alone and should therefore be considered—when possible, based on geographical regulations—the treatment of choice for infrabony defects. The selection of the type of BG (autogenous, allogeneic, xenogeneic or synthetic BG) and the type of biologic agent (EMD, PRF, PRP or rhPDGF-BB) plays an important role on the final results, with rhPDGF-BB and PRF associated with superior clinical and radiographic outcomes compared to PRP and EMD, and rhPDGF-BB exhibiting the largest effect size for most parameters.

### 5.2 | Implications for future research

There is a need for clinical trials on the treatment of infrabony defects reporting individual patient-level data

on patient characteristics and morphology of the defect, together with clinical, radiographic, esthetic, wound healing, and PROMs. Future NMAs could significantly benefits from high quality individual patient level data to further explore multiple comparisons among treatment strategies and the role of effect modifiers on the regenerative outcomes of infrabony defects. Future applications of biologics that should be further explored include the nonsurgical treatment of infrabony defects, as showed by newer investigations reporting promising outcomes.[73,234] Lastly, clinical trials incorporating cost-analysis and PROMs when utilizing different biomaterials are encouraged.

## AUTHOR CONTRIBUTIONS

LT, CYC, and DK designed the study; LT and CYC performed the literature search, initial screening, and article selection; LT and CYC extracted the data and assessed the risk of bias; SB contributed to the study methodology and conducted the statistical analysis; LT led the writing; and CYC, DK, and SB revised the manuscript.

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## CONFLICTS OF INTEREST

The authors report no conflicts of interest related to the conduction of this systematic review.

## FOOTNOTES

‡ RStudio, Version 1.3.959, Boston, MA, USA.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supplementary Appendix in the online *Journal of Periodontology*.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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