Received: 20 June 2022 | Revised: 23 September 2022 | Accepted: 23 September 2022

DOI: 10.1002/JPER.22-0361

JOURNAL OF Periodontology

BEST-EVIDENCE CONSENSUS

American Academy of Periodontology best evidence consensus statement on the use of biologics in clinical practice

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Abstract

A biologic is a therapeutic agent with biological activity that is administered to achieve an enhanced regenerative or reparative effect. The use of biologics

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has progressively become a core component of contemporary periodontal practice. However, some questions remain about their safety, indications, and effectiveness in specific clinical scenarios. Given their availability for routine clinical use and the existing amount of related evidence, the goal of this American Academy of Periodontology (AAP) best evidence consensus (BEC) was to provide a state-of-the-art, evidence-based perspective on the therapeutic application of autologous blood-derived products (ABPs), enamel matrix derivative (EMD), recombinant human platelet-derived growth factor BB (rhPDGF-BB), and recombinant human bone morphogenetic protein 2 (rhBMP-2). A panel of experts with extensive knowledge on the science and clinical application of biologics was convened. Three systematic reviews covering the areas of periodontal plastic surgery, treatment of infrabony defects, and alveolar ridge preservation/reconstruction and implant site development were conducted a priori and provided the foundation for the deliberations. The expert panel debated the merits of published data and exchanged experiential information to formulate evidence-based consensus statements and recommendations for clinical practice and future research. Based on an analysis of the current evidence and expert opinion, the panel concluded that the appropriate use of biologics in periodontal practice is generally safe and provides added benefits to conventional treatment approaches. However, therapeutic benefits and risks range based on the specific biologics used as well as patient-related local and systemic factors. Given the limited evidence available for some indications (e.g., gingival augmentation therapy, alveolar ridge preservation/reconstruction, and implant site development), future clinical studies that can expand the knowledge base on the clinical use of biologics in periodontal practice are warranted.

KEYWORDS
alveolar ridge preservation, biologics, implant site development, periodontal plastic surgery, periodontal regeneration, periodontal therapy

INTRODUCTION

In 2016, the American Academy of Periodontology (AAP) embarked on a best evidence consensus (BEC) model of scientific inquiry to address questions of clinical importance in the treatment of periodontal and peri-implant diseases and conditions. Three BECs have been conducted in the past on the following topics: cone beam computed tomography imaging,[1] laser therapy,[2] and periodontal and peri-implant phenotype modification.[3] This most recent BEC focuses on the use of biologics in contemporary periodontal practice.

The ultimate objective of periodontal and implant-related therapy is to preserve, improve, reconstruct, and maintain the tissues that provide support to teeth and dental implants to achieve predictable, successful, and long-lasting health, comfort, function, and esthetics.[4] To overcome some of the limitations of conventional therapeutic approaches, clinicians have leveraged tissue engineering concepts to enhance the outcomes of periodontal therapy in daily practice since the late 1990s. Over the past three decades, different bioengineering strategies to stimulate new oral tissue formation, including the use of biologic agents, have been described and tested in preclinical and clinical settings.[5]

According to the Food and Drug Administration (FDA), a "biological product" (biologic) is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of a disease or condition of human beings."[6] In the field of oral tissue regeneration, the term "biologic" can be more narrowly

defined as a therapeutic agent with biological activity that is administered to achieve an enhanced regenerative or reparative effect.[7]

Biologics can be subclassified into stem cells, gene therapy agents, autologous blood-derived products (ABPs), and bioactive factors, such as enamel matrix derivative (EMD), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), bone morphogenetic proteins (BMPs), growth and differentiation factor 5 (GDF-5), and teriparatide (PTH 1-34).[8] Given their availability for regular clinical use in dental practice and the existing amount of related literature for different therapeutic applications, the goal of this BEC was to provide an updated and evidence-based perspective on the current therapeutic use of ABPs, EMD, recombinant human platelet-derived growth factor BB (rhPDGF-BB), and recombinant human bone morphogenetic protein 2 (rhBMP-2) for the treatment of mucogingival deformities and periodontal infrabony defects, and for alveolar ridge preservation (ARP) or reconstruction (ARR) after tooth extraction and implant site development (ISD), including horizontal/vertical alveolar ridge augmentation (ARA) and maxillary sinus floor augmentation (MSFA) with simultaneous or delayed implant placement.

For each focused clinical question addressed below, there is an adequate amount of evidence available. However, by itself, that evidence is, in the judgment of the expert panel convened by the AAP, insufficient to support broad conclusions and/or clinical practice guidelines. Each periodontist should make an independent decision regarding use of biologics in the treatment of individual patients based on that periodontist's conclusions regarding the utility of biologics and the needs of the patient in question.

Members of the expert panel of this BEC, however, have extensive knowledge of biologics and experience in their use in contemporary clinical periodontal practice. Specific clinical questions were posed, and systematic reviews were performed a priori to address each of these questions. The expert panel then convened, debated the merits of published data and experiential information, and developed consensus statements based on the best evidence available.

FOCUSED CLINICAL QUESTION 1

What is the effect of using biologics (i.e., ABPs, EMD, or rhPDGF-BB) on the outcomes of root coverage and gingival augmentation therapy?

Evidence search strategy and results

An electronic search of MEDLINE (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases as well as a manual search of articles published from four specialized journals (*Journal of Periodontology*, *Journal of Clinical Periodontology*, *Journal of Periodontal Research*, and *International Journal of Periodontics and Restorative Dentistry*) yielded 1393 articles published in English from January 1, 2000 to September 30, 2021. Among these, a full-text assessment was performed on 85 articles. A total of 48 trials reported in 55 articles met the inclusion criteria and were analyzed qualitatively with 24 articles providing data for the conduction of network meta-analyses. All selected articles reported on the topic of root coverage therapy.

Evidence-based conclusions

According to current available evidence and within the limitations of a systematic review prepared prior to the consensus conference, the following conclusions can be drawn from the frequentist mixed-modeling approach to network meta-analysis[9]:

1. Biologics (i.e., ABPs, EMD, and rhPDGF-BB) used in conjunction with coronally advanced flaps (CAFs) for root coverage purposes promote statistically and clinically significant improvements respective to baseline clinical parameters, specifically in terms of recession depth (RD) reduction, clinical attachment level gain, and keratinized tissue width (KTW) gain. Notably, KTW gains were more evident in sites treated with ABPs or rhPDGF-BB.

2. The adjunctive use of ABPs and EMD does not provide substantial additional improvement in terms of clinical and patient-reported outcome measures (PROMs) to those achieved by CAFs alone when baseline KTW is >2 mm.

3. Both platelet-rich fibrin (PRF) + CAF and EMD + CAF rendered inferior mean root coverage (MRC%), complete root coverage (CRC%), RD reduction, and KTW gain compared to subepithelial connective tissue graft (SCTG) + CAF, which should still be considered the "gold standard" in root coverage therapy. Regarding the use of rhPDGF-BB + CAF, although available studies have reported equivalent results compared to the gold standard intervention, limited evidence precludes formal comparisons with CAFs or SCTG + CAF.

Expert opinion

The panel spent considerable time in discussion to arrive at a consensus on the effect(s) of biologics on the outcomes of periodontal plastic surgery. The panel recognized that there are certain areas for which there is limited clinical evidence (e.g., gingival augmentation therapy).

The following statements summarize the consensus of the panel of experts:

1. Adjunctive use of biologics enhances initial postoperative healing after root coverage and gingival augmentation therapy.
2. Autogenous SCTG remains the gold standard in bilaminar root coverage procedures.[10] When SCTG is not selected, clinicians may consider soft tissue graft substitutes (e.g., xenografts or allografts) combined with a biologic.
3. The safety of ABPs, EMD, and rhPDGF-BB in the context of root coverage therapy is well documented, and there are no known therapeutic downsides to their routine use in clinical practice.

Benefits

1. Biologics can promote soft tissue healing and reduce the incidence of postoperative complications.
2. After the use of biologics in appropriate situations, patients may experience less postoperative pain and reduced need for analgesics.
3. Biologics may increase predictability of treatment in patients undergoing root coverage and gingival augmentation therapy that have delayed/impaired healing (e.g., smokers/vapers or individuals with uncontrolled systemic diseases known to affect wound healing).
4. Biologics may contribute to improved outcomes following treatment or retreatment of complex gingival recession defects (e.g., sites presenting interproximal attachment loss, limited baseline KTW, and/or thin gingival tissue).[11,12]
5. The therapeutic benefits of using biologics in root coverage procedures are maximized when used in a bilaminar/combination approach, in conjunction with a graft.
6. If an allograft or a xenograft is selected for a bilaminar approach instead of autogenous tissue (e.g., treatment of multiple recession defects or medical contraindications), limited evidence suggests that the use of biologics provides an adjunctive benefit.
7. Biologics offer the potential for periodontal regeneration in the context of mucogingival therapy. Evidence of periodontal regeneration exists with EMD and rhPDGF-BB either alone or in combination with grafts, scaffolds, or matrices.

FOCUSED CLINICAL QUESTION 2

What is the effect of using biologics (i.e., ABPs, EMD, or rhPDGF-BB) on the outcomes of surgical therapy of infrabony defects?

Evidence search strategy and results

An electronic search of MEDLINE (via PubMed), EMBASE, and CENTRAL databases as well as a manual search of titles and abstracts from six specialized journals (*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*) yielded 385 relevant articles published in English from January 1, 2000 up to December 31, 2021. Full-text assessment was performed on 182 articles. A total of 153 articles met the inclusion criteria and were analyzed qualitatively, with 150 studies providing data for the conduction of network meta-analyses.

Evidence-based conclusions

According to current available evidence and within the limitations of a systematic review prepared prior to the consensus conference, the following conclusions can be drawn from the frequentist mixed-modeling approach to network meta-analysis:[13]

1. The use of biologics (i.e., ABPs, EMD, and rhPDGF-BB) may significantly enhance the clinical and radiographic outcomes after the surgical treatment of infrabony defects.
2. rhPDGF-BB and PRF are associated with superior clinical and radiographic outcomes compared to EMD and platelet-rich plasma (PRP).
3. Combination therapies involving bone grafts, either with a biologic or barrier membrane, are the most effective strategies for the treatment of infrabony defects. However, the use of membranes with biologics should be avoided when graft containment is feasible since their combined use may prevent some of the benefits associated with the use of biologics (i.e., chemotaxis for pluripotential mesenchymal cell migration from soft tissue niches).

4. Allogeneic and xenogeneic bone grafts are associated with greater clinical benefits regarding clinical outcomes than autogenous and synthetic bone grafts.
5. Xenogeneic bone grafts with rhPDGF-BB or PRF are the best combination therapy to maintain the stability of the gingival margin following regenerative treatment of periodontal infrabony defects.

Expert opinion

The panel spent considerable time in discussion to arrive at a consensus on the effect(s) of ABPs, EMD, and rhPDGF-BB on the outcomes of regenerative therapy of infrabony defects.

The following statements summarize the consensus of the panel of experts:

1. The ultimate goal of interventions for the treatment of infrabony periodontal defects is to achieve periodontal regeneration (new periodontal ligament, new cementum, new bone, and new connective tissue attachment) and promote long-term periodontal health.
2. Histological evidence of regeneration has been demonstrated after the topical application of rhPDGF-BB or EMD. Sites that heal via regeneration may have better long-term stability compared to those that heal by repair (long junctional epithelium).
3. Biologics are effective for the treatment of periodontal infrabony defects in terms of radiographic and clinical outcomes with added benefits when they are combined with biocompatible/biodegradable scaffolds (e.g., xenografts, allografts).
4. Biologics can be used with either conventional or minimally invasive flap approaches.
5. Long-term data (5+ years) pertaining to the use of some biologics (e.g., rhPDGF-BB and EMD) for the treatment of periodontal infrabony defects are available.
6. The safety of using biologics (i.e., ABPs, EMD, and rhPDGF-BB) for the treatment of infrabony periodontal defects is well documented, and the therapeutic benefits outweigh potential risks.

Benefits

1. The use of biologics may increase the predictability of surgical interventions for the treatment of infrabony defects through promotion and acceleration of healing and regeneration, reduced risk of postoperative complications, and improved treatment outcomes as evidenced by clinical and radiographic outcomes reported in the literature.
2. Some biologics (e.g., ABPs) may improve handling of bone graft materials.
3. Biologics can be used in minimally invasive regenerative procedures to avoid the elevation of extensive flaps associated with the use of membranes, to simplify the surgical technique, and to reduce trauma.
4. Superior long-term stability, periodontal health, and esthetics after surgical treatment of infrabony defects have been demonstrated with the use of some biologic agents (i.e., EMD and rhPDGF-BB).

FOCUSED CLINICAL QUESTION 3

What is the effect of using biologics (i.e., ABPs, EMD, rhPDGF-BB, or rhBMP-2) on the outcomes of ARP/ARR and ISD?

Evidence search strategy and results

An electronic search of MEDLINE (via PubMed), EMBASE, and CENTRAL databases was conducted. Bibliographies of the identified articles as well as previously published systematic reviews on the topic were also searched. These searches yielded 3044 relevant articles published in English from January 1, 2000 up to November 1, 2021. Among these, a full-text assessment was performed on 90 articles. A total of 39 articles met the inclusion criteria and were analyzed qualitatively in addressing this question (18 in ARP/ARR, 9 in ARA, and 8 in MSFA). Due to the significant heterogeneity across articles (e.g., discrepancies between experimental and control therapies across studies, diversity of biologics employed, and different surgical approaches), a quantitative synthesis of the data reported in the included studies and, consequently, a meta-analysis could not be completed. Instead, a descriptive but thorough analysis of the reported outcomes was performed. It is important to highlight that some studies reported the off-label usage of biologics.

Evidence-based conclusions

According to current available evidence and within the limitations of the commissioned systematic review prepared prior to the consensus conference,[14] the following conclusions can be drawn:

1. There is limited evidence to support that the use of ABPs, EMD, rhPDGF-BB, or rhBMP-2—either as a monotherapy or in combination with graft materials

for ARP/ARR and ISD—renders superior clinical and radiographic outcomes when compared with conventional interventions.
2. On the other hand, the adjunctive use of these biologics seems to translate into favorable histomorphometric outcomes (i.e., mineralized tissue formation observed in bone core biopsies).
3. Although PROMS were underreported in the selected articles, it seems that they are minimally improved by the use of biologics.

Expert opinion

The expert panel acknowledged the difficulty in drawing specific conclusions from the information provided in the systematic review due to the limited evidence available on the use of ABPs, EMD, rhPDGF-BB, and rhBMP-2 in ARP/ARR and ISD procedures. As a result, the panel spent considerable time in discussion to arrive at a consensus as well as to make recommendations for clinical practice and future research.

The following statements summarize the consensus of the panel of experts:

1. The use of biologics (i.e., ABPs, EMD, rhPDGF-BB, and rhBMP-2) may enhance osteogenesis when combined with biocompatible/biodegradable scaffolds (e.g., xenografts, allografts, alloplasts) in ARP/ARR and ISD procedures.
2. The benefits of using biologics generally increase with the complexity of the defect (e.g., noncontained, large defects).
3. The safety of biologics for ARP/ARR and ISD is well documented, and there are no major contraindications to routine use in clinical practice. However, it must be noted that rhBMP-2 has been associated with localized swelling after treatment. Hence, the use of rhBMP-2 requires careful presurgical assessment.

Benefits

1. Biologics may promote soft tissue healing and bone formation, which may be particularly beneficial in situations where poor healing outcomes are anticipated (e.g., diabetic patients or smokers).
2. The use of biologics may simplify and expedite the surgical treatment (e.g., no autogenous tissue harvest, no barrier membrane, smaller or without a flap) as well as reduce total treatment time, need for ancillary bone augmentation at the time of delayed implant placement, proportion of remaining bone graft substitute, need for retreatment, and risk of postoperative complications.
3. Some biologics (e.g., ABPs) may improve handling of bone graft materials.

OVERARCHING STATEMENTS

Limitations

According to the panel of experts, the general limitations of biologics are the following:

- Results may vary largely depending on case selection, technical execution, and/or graft materials used.
- The cost-benefit ratio for their use must be considered, particularly in less challenging clinical scenarios.

Additionally, ABPs require:

- Venipuncture
- Training of auxiliary personnel
- Specific equipment and disposables
- Additional preparation/surgical time

Clinicians should also note that various preparation protocols for ABPs and patient-related factors may result in differences in the biological properties of the final product, which may affect the outcomes of therapy.

Potential risks

There are no known reported risks associated with the clinical application of biologics (ABPs, EMD, rhPDGF-BB, and rhBMP-2) when used as monotherapies or in combination with autogenous grafts or scaffolds for the treatment of mucogingival deformities, infrabony defects, ARP/ARR and ISD purposes; however, according to the panel of experts, a robust, dose-dependent local inflammatory reaction may occur after the use of rhBMP-2.

Clinical practice recommendations

Clinicians should consider the use of biologics in:

1. Patients who exhibit compromised wound healing potential (e.g., uncontrolled diabetes mellitus, smokers/vapers, etc.).
2. Defects presenting features associated with lower predictability (e.g., thin periodontal phenotype, root prominence, shallow vestibular depth, complex

noncontained infrabony defects, extraction sites exhibiting extensive structural damage, or large vertical ridge defects).
3. Clinical situations where the promotion of ideal soft tissue healing is crucial (e.g., esthetic zone) and where limited surgical access is required (e.g., contained infrabony defect).
4. Clinical situations where a shortened healing timeframe would be advantageous (e.g., orthodontic therapy following the correction of the mucogingival deformity and/or establishment of periodontal stability, prosthetic considerations for key abutment teeth, etc.),
5. Patients with a history of therapy failure or unsatisfactory results after conventional treatment approaches.

Future research recommendations

Future research on the use of biologics in periodontal practice should:

1. Prioritize the conduction of well-designed randomized controlled trials with acceptable surgical protocols, detailed characterization of the defects treated, standardized outcome measures and data collection methods (not limited to clinical and radiographic parameters but also including esthetic outcomes and PROMs) to determine the benefits of using biologics compared to conventional therapies and facilitate the conduction of future high-level quantitative analyses (e.g., network meta-analyses). There is also a need for head-to-head comparative studies among different biologics and/or other regenerative strategies (e.g., cell therapy).
2. Investigate the effect of biologics on the outcomes of periodontal therapy as a function of different variables (e.g., systemic status, smoking habits, baseline phenotypic characteristics, presence and extent of interproximal tissue loss, flap design, graft material employed, use of magnification and microsurgical instruments, etc.) to gather information that can be effectively used to optimize case selection and treatment protocols in daily clinical practice.
3. Elucidate whether the addition of biologics to the "gold standard" treatment (e.g., SCTG+CAF for root coverage) can further enhance the outcomes of therapy, particularly in challenging clinical scenarios.
4. Precisely define the risks, benefits, and efficacy of using biologics with different scaffolding matrices to provide a better understanding of wound healing kinetics at the cellular and tissue level as well as other wound repair outcomes.
5. Involve the application and validation of novel non-invasive technologies (e.g., biomarkers and advanced imaging, such as ultrasonography and laser speckle contrast) to assess structural features (e.g., soft tissue thickness, bone crest position, alveolar ridge volume) and monitor biological events (e.g., angiogenesis, bone turnover) after the use of biologics.
6. Result in the publication of long-term (5+ years) large datasets to assess biological safety and determine the stability of the outcomes obtained after the use of biologics as well as to perform artificial intelligence-driven assessment of big data, which may augment conclusions drawn from meta-analyses consistent with personalized/precision medicine approaches.
7. Explore the development of streamlined and standardized ABP preparation protocols.
8. Test the safety and efficacy of novel biologics with therapeutic potential for different clinical applications.

CONSENSUS CONCLUSIONS BASED ON EVIDENCE

- The use of biologics in periodontal practice is generally safe.
- Therapeutic benefits and risks vary based on the specific properties of biologics and on patient-specific local and systemic factors.
- There is adequate evidence on the effectiveness of using biologics with scaffolds in specific clinical indications (e.g., root coverage therapy and treatment of infrabony defects).
- Limited clinical evidence is available for some indications (e.g., gingival augmentation therapy, ARP/ARR, and ISD), which highlights the need for further scientific research in this area.

CONSENSUS CONCLUSIONS BASED ON EXPERT OPINION

- Biologics may provide added benefits to conventional treatment approaches.
- Expected benefits for the use of biologics increase with the complexity of the defect to be treated.
- Surgical time may be reduced when using off-the-shelf biologics compared to autologous products.
- Although the application of biologics may be particularly beneficial in clinically challenging scenarios, as they may simplify surgical procedures and increase predictability, their use should be applied more judiciously in less complex clinical situations.
- Clinicians should take into consideration relevant aspects pertaining to case selection, such as patient-related local and systemic factors, medications, habits

(e.g., smoking/vaping), and cost-benefit ratio, prior to making a clinical recommendation regarding the use of biologics.
- Use of biologics does not replace the need for meticulous planning and execution of the surgical intervention.

ACKNOWLEDGMENTS

The American Academy of Periodontology's 2022 Best Evidence Consensus Meeting on the Use of Biologics in Clinical Practice was sponsored by BioHorizons (Birmingham, Alabama), Geistlich Biomaterials (Princeton, New Jersey), Lynch Biologics (Franklin, Tennessee), and Straumann USA (Andover, Massachusetts).

CONFLICTS OF INTEREST

Participants filed detailed disclosure of potential conflicts of interest relevant to the meeting topic, and these are kept on file.

The authors receive, or have received, advisor fees and/or lecture compensation from the following companies: BioHorizons, Inc.; Geistlich; Lynch Biologics; McGuire Institute; Osteogenics, Inc.; and Straumann. Jeanne Ambruster is CEO at The Avenues Company. Katie Goss is executive strategist for communications, science, and organizational growth at the American Academy of Periodontology.

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How to cite this article: Avila-Ortiz G, Ambruster J, Barootchi S, et al. American Academy of Periodontology best evidence consensus statement on the use of biologics in clinical practice. *J Periodontol*. 2022;93:1763–1770. https://doi.org/10.1002/JPER.22-0361