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REVIEW ARTICLE

Complications and treatment errors related to regenerative periodontal surgery

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1 | RATIONALE FOR REGENERATIVE PERIODONTAL THERAPY

The main goal of periodontal therapy is to treat the infection caused by periodontal pathogenic biofilm and to arrest or slow down further attachment and bone loss, ultimately preventing tooth loss. Successful treatment is defined clinically by reduction of probing pocket depths (PPD), resolution in inflammation (i.e., resolution of suppuration and reduction of bleeding scores) along with the reformation of a dento-gingival environment that allows effective oral hygiene measures. Ideally, these clinical improvements should be also accompanied by gain of clinical attachment level (CAL) and radiographic bone gain. There is ample evidence that in the great majority of cases, these goals can be achieved with the first and second step of periodontal treatment consisting of patient motivation and instruction for successful removal of supragingival dental biofilm and control of risk factors known to be associated with the deterioration of periodontal status such as smoking, and diabetes (step one) followed by nonsurgical subgingival instrumentation (step two).[1]

However, in particular areas/defects, the endpoints of therapy defined as no periodontal pockets ≥4–5 mm with bleeding or residual probing depths ≥6 mm, are not always achieved following steps one and two. For such deep sites which persist after completion of steps 1 and 2, further treatment (i.e., the so-called step three) is needed, in order to reach the treatment endpoints, and thus enable the patients to be enrolled in a periodontal maintenance program (i.e., step 4) to prevent recurrence of the disease. Based on the individual case and defect, step 3 may consist of a surgical access (i.e., either conventional, resective, or regenerative) aiming to facilitate subgingival instrumentation, and to either resect or regenerate the residual soft and hard tissues to re-establish an environment favorable for proper supragingival biofilm control.

In the presence of deep intrabony (angular) defects and class II molar furcation involvements, resective surgery may lead to relevant clinical improvements by decreasing deep pockets to a more maintainable range, but the healing is accompanied by substantial loss of attachment and increase in soft tissue recessions. Therefore, it is generally recommended that residual deep pockets associated with angular bony defects with an intrabony component ≥3 mm or deeper and class II mandibular and buccal maxillary furcations are rather treated by means of regenerative periodontal surgery than via a resective approach[1] (Figures 1 and 2).

Regenerative periodontal surgery includes the use of specifically designed surgical techniques aiming at maximally preserving the periodontal tissues followed by the application of various biomaterials which facilitate the regeneration of the tooth's supporting tissues (i.e., root cementum, periodontal ligament, and bone), ultimately leading to probing depth reduction, gain of clinical attachment, and only limited recession.[2-4]

It is recommended that the selection of biomaterials used for periodontal regeneration is based on well-defined biologic and clinical criteria such as availability of solid preclinical research identifying plausible mechanism(s) of action leading to periodontal regeneration and evidence of efficacy supported by human histology and randomized controlled clinical trials. Based on these criteria, at present, the best-documented biomaterials used for regenerative periodontal surgery are guided tissue regeneration (GTR) using non-bioresorbable or bioresorbable membranes, and an enamel matrix

Karin Jepsen and Anton Sculean contributed equally to this article.

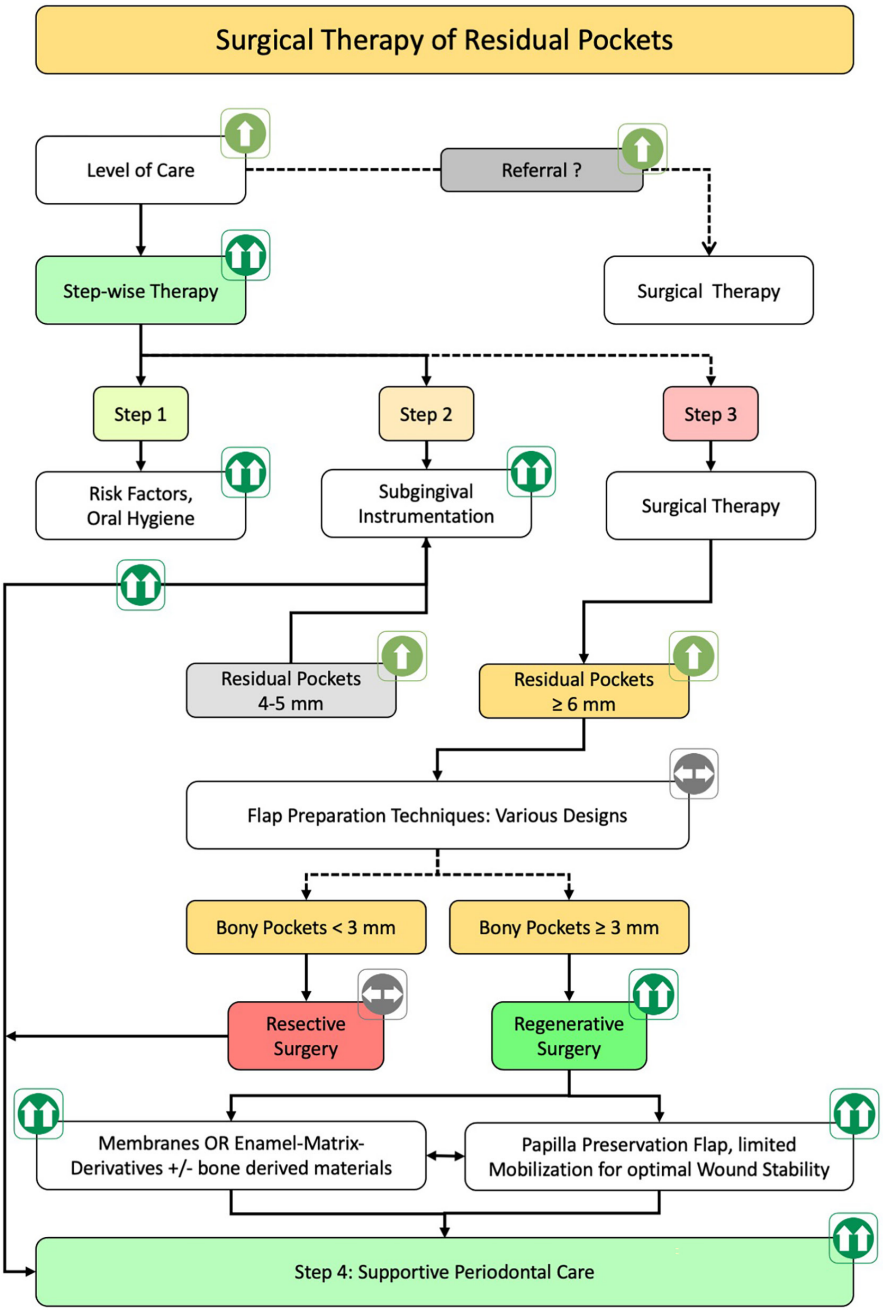

FIGURE 1 Flowchart illustrating the indication for regenerative surgery in intrabony defects. This flowchart was created by DG PARO as an adapted version of the original publication.[1] Courtesy of Prof. Henrik Dommisch.

derivative (EMD), both concepts being used with or without bone grafting materials.[1–4]

A recently published systematic review has analyzed the clinical, radiographic, and patient-reported outcomes (PROMs) in intrabony defects treated with regenerative surgery or access flap alone. The analysis was based on a total of 79 RCTs resulting in 88 articles published from 1990 to 2019 summarizing the outcomes in 3042 patients and 3612 intrabony defects, respectively.[3] The results provided substantial evidence on the adjunctive clinical benefit of regenerative procedures in terms of CAL gain compared with access flap alone. Treatment with access flap in conjunction with either EMD or GTR were superior to access flap alone in improving CAL (1.27 mm; 0.79–1.74 mm and 1.43 mm; 0.76–2.22, respectively). Among grafting materials, the addition of deproteinized bovine bone mineral (DBBM) improved the clinical outcomes of both GTR with resorbable barriers and EMD. Interestingly, the analysis has also revealed that papillary preservation flaps additionally enhanced the clinical outcomes compared to conventional access flaps, thus suggesting that they should be the preferred surgical approach, when intrabony defects are treated with a regenerative procedure.[1]

The clinical performance of regenerative periodontal surgery for the treatment of furcation defects as compared with access flap alone has also been recently analyzed in a systematic review consisting of 19 articles reporting on 20 RCTs (19 on class II, 1 on class III furcations) comprising a total of 575 patients and 787 defects, respectively.[4] The results have provided evidence for the superior

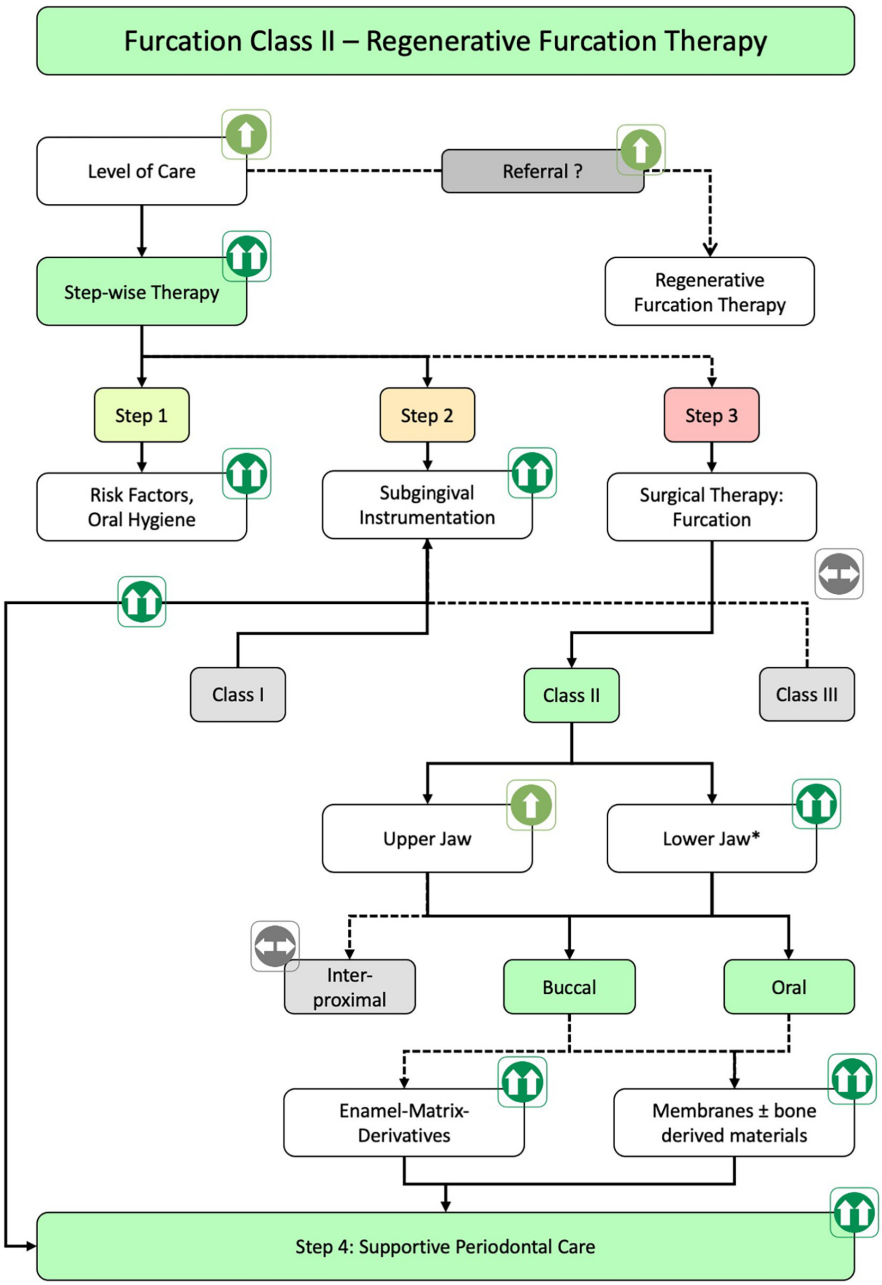

FIGURE 2 Flowchart illustrating the indication for regenerative surgery furcation defects. This flowchart was created by DG PARO as an adapted version of the original publication.[1] Courtesy of Prof. Henrik Dommisch.

outcomes obtained with a regenerative approach over access flap alone. Interestingly, bone replacement grafts (BRG) resulted in the highest probability (Pr = 61%) of yielding the best outcomes in terms of horizontal bone level (HBL) gain while the combination of nonresorbable membranes + BRG resulted in the best outcomes in terms of vertical clinical attachment (VCAL) gain (Pr = 75%) and probing pocket depth reduction (Pr = 56%). From a clinical point of view, the treatment goal in class II furcations is defect closure or conversion of a class II furcation into a class I (furcation improvement). Because the odds ratio for furcation improvement is 20.9, it is generally recommended that in step 3, class II furcation defects are rather treated by means of a regenerative approach than by access flap alone.[1,4]

However, despite the ample evidence suggesting a substantial clinical benefit in intrabony and class II furcation defects following the use of regenerative procedures, the clinical outcomes are strongly influenced by a number of factors, that can lead to complications, which, in turn, may jeopardize the outcomes. Ignoring these factors can lead to failures in decision-making and execution of treatment, what may be considered as treatment errors.

2 | FACTORS INFLUENCING THE OUTCOMES OF REGENERATIVE PERIODONTAL SURGERY

Complications and treatment errors in regenerative periodontal surgery may be related to a number of factors on the level of the patient, the tooth/defect, and the operator.[5] Paying close attention to these factors in case selection, treatment planning, and execution will help to avoid treatment errors and to minimize complications.

2.1 | Patient factors/patient selection

2.1.1 | Infection control

Since steps one and two of periodontal therapy have been repeatedly shown to represent the most important steps in periodontal treatment, it is reasonable to emphasize that regenerative periodontal surgery should only be considered after completion of step 1 and 2 followed by reevaluation.[1]

There is ample evidence from the literature supporting the fact that the short and long-term success after any type of periodontal surgery is strongly dependent on the level of infection control (i.e., level of oral hygiene) and regular maintenance care. Periodontal surgery performed in a so-called "dental biofilm or plaque-infected" dentition will fail to provide the desired clinical outcomes,[6,7] while on the contrary, any type of surgical procedure may lead to clinical improvements if appropriate infection control in ensured.[7] Later, multiple studies on surgical periodontal intervention have shown a dose-dependent effect of plaque control on healing outcomes.[5,8,9]

The current EFP S3-Level Clinical Practice Guideline recommends not to perform periodontal surgery in patients lacking adequate levels of self-performed oral hygiene.[1]

The level of self-performed oral hygiene is usually assessed using a plaque control record (for an example, see ref. 10). Robust evidence indicates that plaque scores lower than 20%–25% are consistently associated with higher clinical improvements following any type of periodontal surgery (i.e., both conventional and regenerative) compared to the outcomes obtained in patients exhibiting higher plaque scores.

Regarding the outcomes of regenerative periodontal surgery, it has been repeatedly demonstrated that substantial clinical improvements and long-term stability following these approaches can only be expected in patients with high levels of oral hygiene and strict maintenance protocols.[8,11] The pivotal role of infection (biofilm) control and regular supportive care for long-term stability following regenerative surgery with GTR, has been elegantly demonstrated by Cortellini et al.[8] Sites treated with GTR had a 50-fold increase in risk of CAL loss between 1 and 4 years in patients who have received only sporadic care, compared with patients enrolled in a regular maintenance program.[8]

Thus, clinicians need to carefully assess the patient's self-performed oral hygiene and provide an adequate individually tailored maintenance program to ensure short and long-term clinical success following regenerative periodontal surgery.[1] Ignoring the importance of a high level of self-performed oral hygiene and not providing the patient with a supportive care program, may thus be viewed as a treatment error.

2.1.2 | Diabetes

Diabetes and smoking are two well-documented risk factors that substantially influence the progression of periodontitis.[12,13] Consequently, diabetes control and smoking cessation/reduction must represent a mandatory part of all phases of periodontitis therapy.[1]

For obvious ethical reasons, no randomized controlled clinical studies have examined the potential effect of uncontrolled diabetes mellitus, well-controlled diabetes, and healthy controls on the outcomes of regenerative surgery. However, a recent prospective cohort study has evaluated the outcomes of minimally invasive regenerative periodontal surgery (MIST)[14] or modified minimally invasive regenerative periodontal surgery (M-MIST)[15] using EMD in patients with and without diabetes.[16] The results have shown comparable outcomes in patients with and without diabetes, thus indicating successful outcomes following regenerative periodontal surgery in patients with controlled diabetes. On the other hand, despite the lack of evidence from controlled clinical studies, it is reasonable to state that regenerative periodontal surgery should not be performed in patients with uncontrolled diabetes. However, in well-controlled diabetic patients, regenerative surgery may represent a viable treatment option, provided that the patients exhibit a good level of oral hygiene and are nonsmokers.

2.1.3 | Smoking

Substantial evidence indicates that smokers present a less favorable response following regenerative periodontal surgery. Tonetti et al.[17] have shown that at one year following GTR therapy, smokers gained significantly less probing attachment level compared to nonsmokers (2.1 ± 1.2 mm compared with 5.2 ± 1.9 mm). A further risk-assessment analysis revealed that smokers had a significantly greater risk than nonsmokers to display a reduced probing attachment level gain following GTR. Comparable results were also reported by Stavropoulos et al.[18] who retrospectively analyzed the factors that may influence the results of GTR with bioresorbable membranes in intrabony defects and found that smokers gained approximately 1 mm less in CAL compared to nonsmokers (3.2 ± 1.4 mm vs. 4.3 ± 1.3 mm, respectively). Moreover, smokers had approximately seven times less chances to gain 4 mm of CAL compared with nonsmokers. Comparable results were also obtained in terms of PPD reduction, which was less pronounced in smokers than in nonsmokers (i.e., 4.5 ± 0.7 mm vs. 5.5 ± 0.7 mm, respectively), yielding deeper residual PPD in smokers than in nonsmokers. These results are in line with those from other studies using regenerative surgery by means of either EMD alone or EMD and bone grafts in intrabony defects,[19] and also in class II molar furcations treated with GTR.[20] A very recent retrospective study has evaluated the five-year results following regenerative periodontal surgery of intrabony defects treated with EMD in patients with different smoking status. At 6 months following regenerative surgery, nonsmokers revealed a greater, but statistically not significant, CAL gain compared to smokers (2.38 ± 2.12 mm vs. 1.50 ± 1.71 mm). At 5 years, however, the site-specific PPD values remained stable in nonsmokers, while smokers showed an increase of 1.60 ± 2.41 mm, thus providing additional

evidence for the negative influence of smoking on the long-term outcomes following regenerative periodontal surgery.[21]

Taken together, the available evidence indicates that smoking impairs the healing outcome of regenerative periodontal surgery irrespective of the surgical technique and regenerative material that is used. Therefore, regenerative periodontal surgery is generally not recommended in smokers (i.e., patients that smoke ≥10 cigarettes/day), and subsequently, clinicians should carefully consider performing regenerative surgery in heavy smokers. As such, not informing the patients about the expected poorer treatment outcomes in heavy smokers may be viewed as treatment error.

Most importantly, in heavy smokers ≥15 cigarettes/day, exhibiting an insufficient level of oral hygiene (Full Mouth Plaque Scores >25%–30%), regenerative surgery should not be considered as a treatment option[1] (Figure 3).

2.2 | Tooth/defect factors

2.2.1 | Mobility

Tooth mobility is considered an important factor for the outcomes of regenerative periodontal surgery, especially regarding its potential influence on blood clot adhesion and wound stability.[22]

A negative and dose-dependent association between tooth hypermobility and the clinical outcomes following regenerative surgery was reported in a number of studies.[23–25] Taken together, the data indicate that on one hand, a high degree of hypermobility (i.e., Miller Degree 3), negatively affects periodontal regeneration, while on the other hand, teeth with limited presurgical mobility responded as favorable to regenerative therapy as nonmobile teeth.[25] Thus, it has been recommended that hypermobile teeth should be splinted before regenerative periodontal surgery.[5] Moreover, recent evidence indicates that even teeth that are severely compromised by advanced intrabony defects and pathological tooth migration respond favorably to regenerative periodontal surgery, provided they were splinted preoperatively and remained splinted by fixed orthodontic appliances until they had reached the desired position.[26–29]

2.2.2 | Endodontic status

It has been recommended that nonvital teeth should receive proper root canal therapy before they can be considered for regenerative surgery,[5] because adequate endodontic treatment did not negatively affect the healing response and the long-term stability of deep intrabony defects treated with GTR.[30] However, combined with other risk factors such as furcation involvement, late complications may occur as shown in (Figure 4).

Thus, based on limited evidence and expert opinion, regenerative surgery of nonvital but endodontically teeth cannot be considered as a treatment error. Still, the question of "prophylactic" root canal treatment of teeth with advanced periodontal destruction reaching the apical third of the root before or right after regenerative surgery remains valid and of practical relevance. In fact, in a study on "hopeless" teeth[31] endodontic treatment was performed on vital teeth before regenerative surgery in situations, where the periodontal lesion also involved the apex.

An example of such a situation that eventually led to complications and tooth loss is illustrated in Figure 5. This undesired outcome of an advanced endo-perio lesion could have possibly been avoided by early endodontic treatment and again emphasizes the importance of patient's compliance with regular monitoring visits.

2.2.3 | Defect morphology

According to current guidelines and supported by robust evidence from a large number of RCTs, teeth with residual deep pockets associated with either intrabony defects (≥3 mm) or mandibular/maxillary class II furcations are candidates for regenerative approaches[1,3,4] (see Figures 1 and 2).

Since defect morphology plays an important role in the healing outcomes following regenerative treatment of intrabony defects,[32–35] the location and extension of the defect together with its morphologic characteristics should be determined presurgically, based on careful analysis of information derived from probing and radiographic data and even from bone sounding.

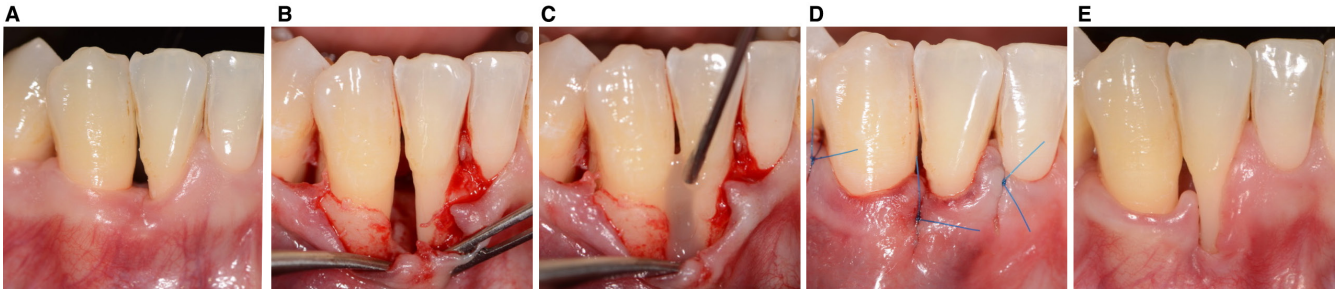

FIGURE 3 Healing complication in a patient with a smoking habit and inadequate plaque control. Preoperative view of area scheduled for regenerative surgery in a heavy smoker. Please also note the biofilm accumulation (A). Intraoperative view depicting the extent of the intrabony defect (B). Application of EMD (C). Flap closure using vertical modified mattress sutures (D). Clinical outcome illustrating a partial loss of the interdental papilla and increased recession (E).

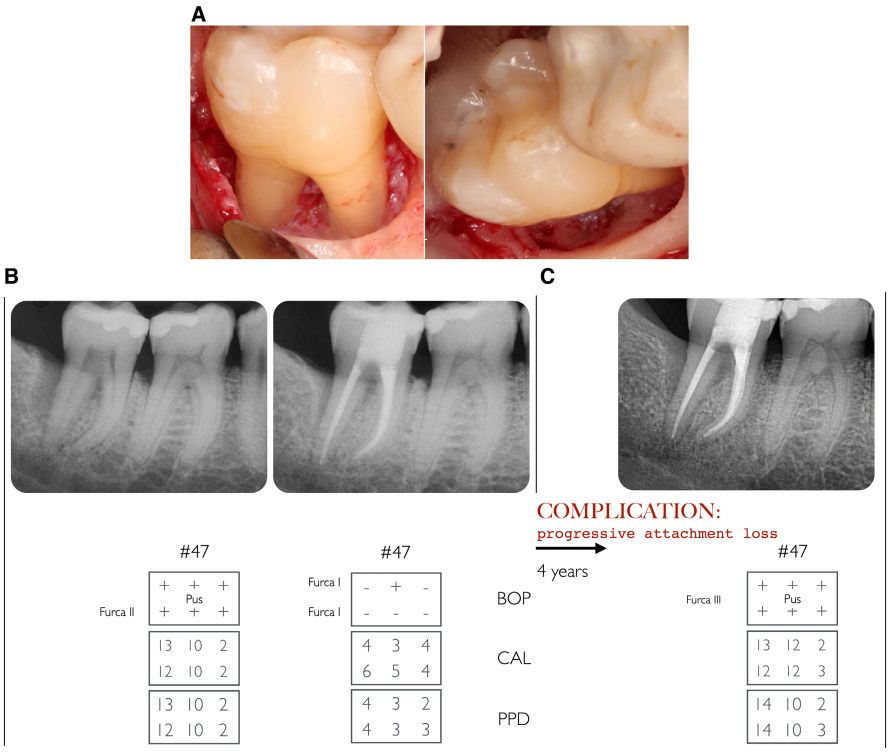

FIGURE 4 Clinical situation of a 53-year-old healthy patient with a periodontal defect at nonvital tooth #47. Root canal treatment was performed and immediately followed by regenerative therapy of an extended combined intrabony/furcation defect (A); Clinical/radiographic 4-year follow-up with clear improvements at 2 years (B); deterioration with progressive horizontal (furcation class III) and vertical attachment loss after 4 years (C).

Intrabony defects

In general, the defect and the width of the intrabony component of the defect are thought to influence the amount of gain of clinical attachment and bone, with narrow and deep defects benefitting the most.[30] Likewise, the number of residual bony walls was shown to be related to the outcomes. The concept of "contained" vs. "noncontained" defects appears to be relevant with regard to the biologically important aspects of space provision, clot adhesion, and wound stability and should be considered in the selection of the most suited biomaterial or combination therapy for a specific defect configuration.[30] In this respect, the choice of the regenerative technology/biomaterial may partially overcome negative morphologic characteristics of intrabony defects. For example, the negative effect of a "noncontained" defect morphology could be diminished by using self-supporting titanium-reinforced barrier membranes.[36]

Furcation defects

While there is substantial evidence to recommend regenerative procedures for mandibular buccal or lingual and mandibular buccal class II furcation defects, the predictability in outcomes is reduced for proximal class II furcation defects, most likely due to difficulties in access, cleansibility, and challenges in wound closure.[1,37] Moreover, various additional local anatomical characteristics have been identified, that will have influence on the outcomes.[33,35,38] These are in particular the location of the roof of the furcation either apical (favorable) or coronal (unfavorable) to the adjacent approximal bone level, but also related to (a) the local soft tissue condition: location of gingival margin in relation to the furcation entrance, the presence of a gingival recession and the gingival phenotype, (b) the vertical bone loss, (c) the distance of restoration margins to the furcation entrance and divergence of the roots. Thus, not all class II furcations are the same, and the likelihood of complications and compromised healing outcomes will depend on the complexity of the individual case. As a consequence, in addition to the simple assessment of furcation class all of the factors described above should be carefully considered in treatment planning and decision-making.

Suprabony defects

The outcomes obtained in suprabony defects treated with access flap surgery with or without the additional application of EMD have been evaluated in a systematic review[39] and have indicated a potential clinical benefit. These results were recently confirmed in a randomized controlled study by Iorio-Siciliano et al.,[40] who have treated 80 patients with suprabony periodontal defects with either access flap and + EMD (test) or access flap alone (control). At 12 months following surgery, mean CAL gain at test sites revealed a statistically significantly higher improvement compared with control sites (i.e., 3.4 ± 0.6 mm vs. 1.8 ± 0.6 mm). Comparable outcomes were also found in terms of PD change ($p = 0.0001$) favoring the use of EMD (i.e., 3.9 ± 0.6 mm vs. 3.2 ± 0.6 mm, respectively). Similar to the improvements of CAL and PD, mean GR was significantly less in the group treated with access flap and EMD compared to treatment with access flap alone (i.e., 0.5 ± 0.7 mm, vs. 1.4 ± 1.0 mm, respectively; $p = 0.001$).

Taken together, the limited available data indicate that in suprabony periodontal defects, regenerative periodontal surgery

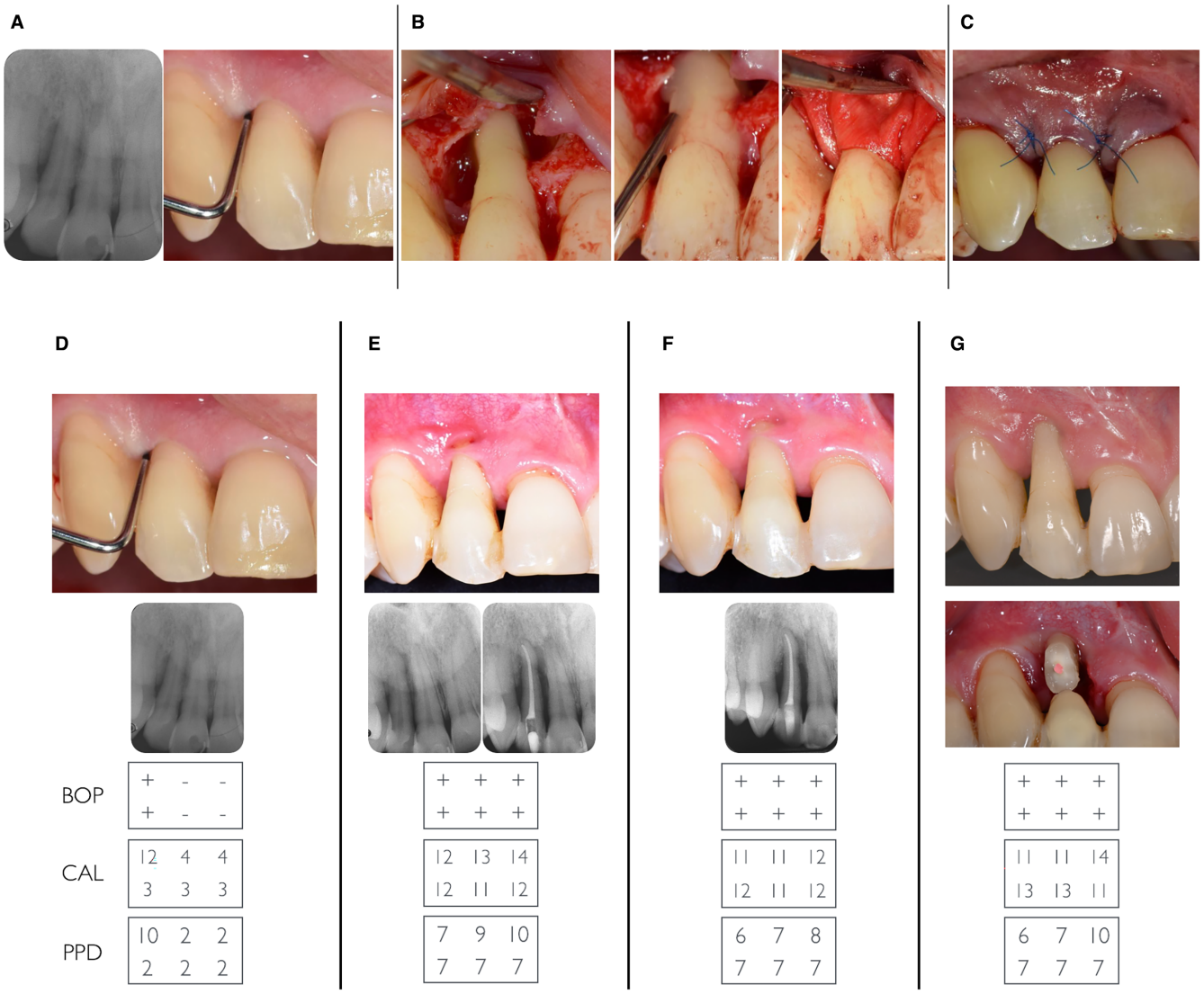

FIGURE 5 Radiographic and clinical situation of an upper lateral incisor in a 49-year-old healthy patient. Deep probing depths at tooth #12 with evidence of extensive bone loss, while pulp sensitivity testing was positive when exposed to chlorethylene and to electric (Vitality Scanner™) scanning (A). A simplified papilla preservation flap technique was performed, using EMD (Emdogain®, Straumann), and a membrane DBBM (BioOss-Collagen®/BioGide®, Geistlich) as regenerative materials (B). Healing was uneventful, monofilic sutures (6–0) were removed after 14 days (C). Five-year follow-up after regenerative surgery on tooth #12. Unfortunately, the patient did not adhere to regular maintenance visits, returned after 2 years complaining about a loose lateral incisor (D). A fenestration of the marginal gingiva of tooth #12 became evident associated with grade 2 mobility and progressive loss of attachment. The tooth was splinted, and root canal treatment was performed (E). The patient wanted to keep his hopeless tooth and chose not to have any more surgery. For maintenance, the root was debrided at unregular recall visits. The situation did not improve (F), and deteriorated after 5 years (G), leading finally to extraction.

with EMD may additionally improve the clinical outcomes compared with access flap alone. However, it is important to note, that this indication is not covered by the current guidelines, because there is no convincing evidence available, demonstrating that horizontal (suprabony) defects/supracrestal components of intrabony defects, or class III furcations can be predictably treated with regenerative periodontal surgery. Thus, such defects should not be selected as primary candidates for regenerative procedures.

2.3 | Surgical factors

2.3.1 | Effect of flap design, instruments, suturing, and operator skills

Flap design

Evidence from preclinical studies has led to a better understanding of the critical role of wound and clot stability as key factors for optimizing the outcomes of regenerative periodontal surgery.[41] The healing

following an optimized flap design by means of papilla preservation technique was evaluated in a randomized clinical study by Retzepi et al.[42] The study compared the gingival blood flow responses following a simplified papilla preservation flap with a conventional modified "Widman" flap by means of Laser Doppler flowmetry. Following local anesthesia and immediately postoperatively, significant ischemia was measured at all sites. A peak hyperemic response was observed on day 1 at the basis of the flap but tended to resolve by day 4 at the sites treated with the papilla preservation approach. However, the hyperemic response persisted until day 7 at the sites treated modified Widman flap thus indicating that papilla preservation flaps are associated with faster postoperative recovery of the gingival blood flow compared with a conventional flap approach (i.e., modified "Widman" flap).[42]

Based on these results, it was suggested that healing of intrabony defects treated by means of flaps that provide primary intention healing and greater wound stability would result in improved clinical outcomes.[19,23,36,43–47]

The current EFP S3-Level Clinical Practice Guideline recommends the use of specific flap designs with maximum preservation of interdental soft tissues such as papilla preservation flaps. Under some specific circumstances limiting flap elevation to optimize wound stability and reduce morbidity is also recommended.[1]

The importance of wound stability on the outcomes of regenerative surgery has been elegantly demonstrated in a randomized clinical trial evaluating a minimally invasive surgical technique as a stand-alone approach or combined with EMD alone or EMD and a bovine bone biomaterial in the management of advanced intrabony defects. The results have failed to show statistically significant differences among the interventions performed with minimally invasive surgery with and without any regenerative materials; all protocols achieved substantial clinical attachment gain and radiographic bone fill.[14,15] Comparable results were recently reported in a clinical study comparing the efficacy of a novel surgical approach designed to better stabilize the entire papilla (i.e., the so-called "entire papilla preservation" technique [EPP]) alone or in combination with EMD plus a bovine-derived bone substitute (EPP + EMD + BS) in the treatment of isolated interdental intrabony defects.[47] The results revealed that the use of EPP with and without regenerative biomaterials resulted in significant amounts of CAL gain and PD reduction, with negligible increase in gingival recession, thus pointing again to the critical importance of flap design to maximize the outcomes of regenerative surgery.

In a very recent systematic review, Simonelli et al.[48] have evaluated the effect of flap design, regenerative technology, and preoperative and postoperative adjunctive protocols on the clinical

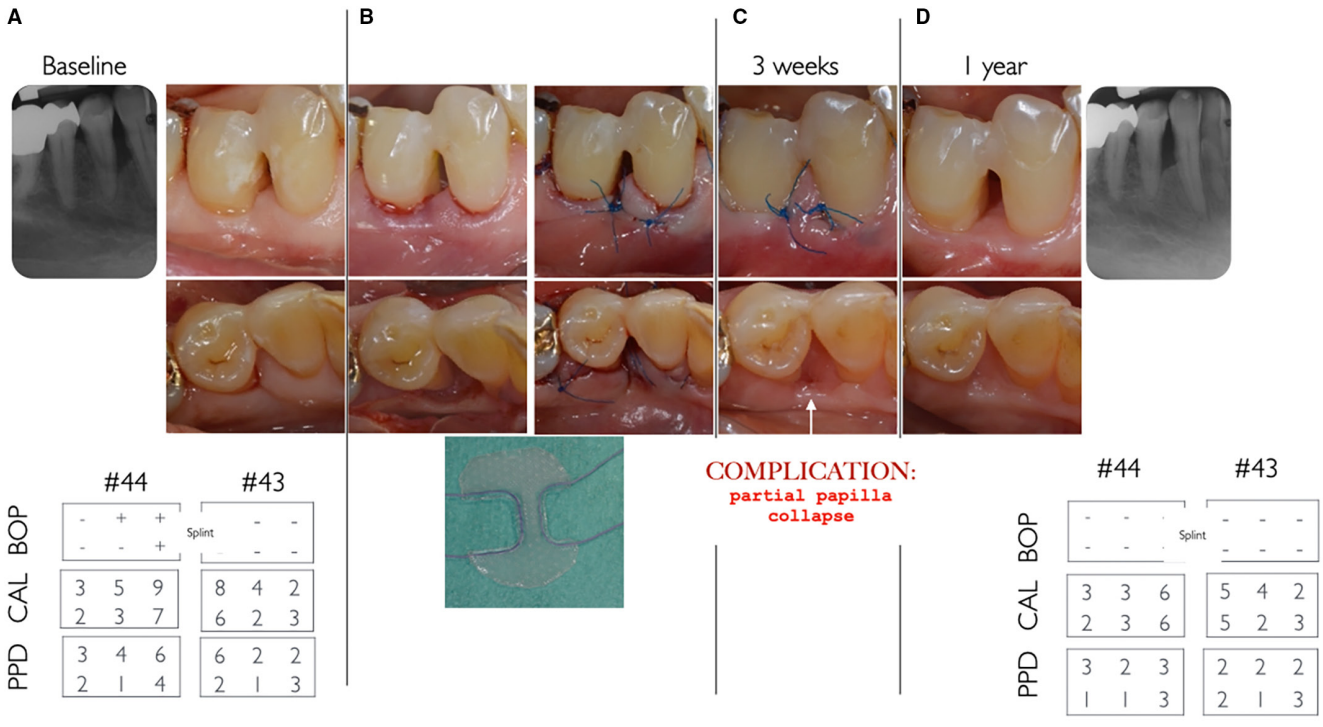

FIGURE 6 Complication with partial collapse/dehiscence of the interdental papilla: radiographic situation and periodontal probings at teeth #44 and #43 taken after step 1 and 2 periodontal therapy (A). The healthy patient was 61 year old, diagnosed with periodontitis stage III, grade B. In step 3 periodontal therapy (B) a resorbable barrier membrane (Guidor, Sunstar), was chosen for regenerating of the intrabony defect located at the mesial of tooth #44. Tooth #44 showed mobility grade 1 and had been splinted to the adjacent tooth #43. Situation at 3 weeks (C) with a slight/partial papilla collapse. After 1 year and after maintenance visits every 3 months, in spite of partial collapse of the interdental papilla the clinical situation was improved indicated by attachment level gain, absence of bleeding on probing, and shallow probing depths. Gingival recession increased with 1–3 mm, but the intraoral radiograph showed hard tissue gain in the vertical defect area (D).

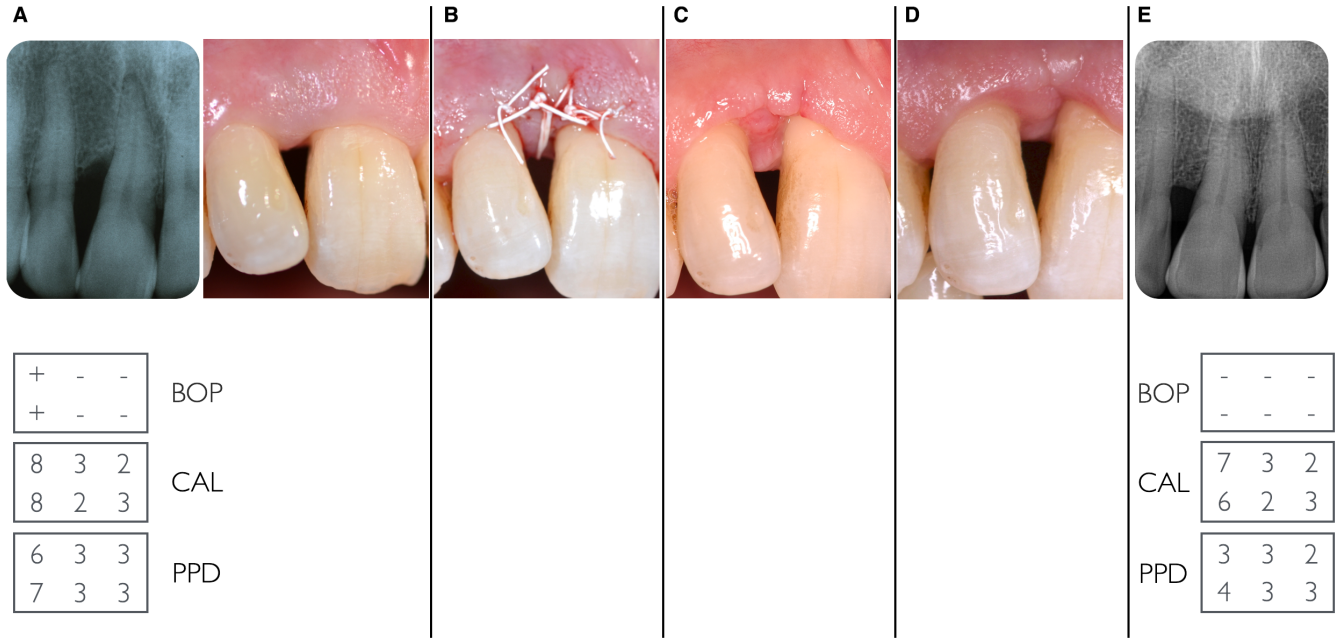

FIGURE 7 Healing complication: collapse of the interdental papilla. Radiographic situation and periodontal probings at tooth #11 following step 1 and 2 of periodontal therapy (A). The healthy patient was 60 years old with a diagnosis of periodontitis stage III, grade B. In step 3 of periodontal therapy a papilla preservation flap plus EMD (Emdogain®, Straumann) was chosen to regenerate the intrabony defect located at the distal of tooth #11. Monofilic sutures (6–0) were used for wound closure (B). Situation 3 weeks after suture removal with a papilla collapsed into the defect, probably due to defect configuration and suture positioning too close to the bony crest (C). After 3 months slight remodeling of the soft tissues, but the patient was not pleased with the aesthetic outcome (D). After 9 years of regular maintenance visits, the clinical situation was improved as indicated by absence of bleeding on probing, shallow probing depths, and resolution of the vertical component of the radiographic defect. However, the patient was still not satisfied with the aesthetic outcome (E).

outcomes and invasiveness. The results, based on the analysis of 13 included trials, indicated that a minimally invasive approach such as the elevation of a single (buccal or lingual) flap positively influenced the intensity of postoperative pain and improved the quality of early wound healing compared with double flaps. The use of a GTR membrane was associated with significantly longer surgery-related chair time and higher postoperative pain, while the adjunctive use of EMD at sites receiving a graft, significantly reduced postoperative pain. An important finding was that open flap debridement performed through the elevation of a single flap may lead to substantial clinical improvements of the lesion with reduced surgery-related chair time and costs, thus representing a promising alternative to the additional use of biomaterials. It needs, however, to be pointed out that at present no histological studies evaluating the nature of the reformed tissues following the use of minimally invasive flaps without application of regenerative biomaterials are available. Moreover, studies on the limitations of minimally invasive flaps in relation to the presurgical conditions (e.g., number of defect walls, defect depths, and defect morphology), are lacking.

Taken together, the available evidence indicates that due to the significant impact of the specific flap design on the outcomes of regenerative surgery, the use of conventional access flap surgery with its potential complications may be viewed as treatment error.

However, if inadequately performed, papilla preservation techniques can also lead to complications in the form of partial collapse, or complete papilla necrosis and subsequent exposure of the regenerative biomaterial (Figures 6 and 7).

Notably, partial collapse does not always result in additional attachment loss or deepening of the sulcus (Figure 6), however depending on the location, the outcome may impair smile aesthetics (Figure 7).

These observations highlight again the need for additional training required by the complexity of regenerative periodontal surgery.

Instruments, visual aids, and suturing

In the last decades, progress in the field of visual magnification has enabled the development of new, less invasive surgical techniques in periodontal regeneration. These so-called "minimally invasive surgical techniques" are characterized by small incisions, limited flap reflection, and suturing for primary wound healing. In intrabony defects, these less invasive surgical procedures have not only yielded favorable clinical outcomes, but have also minimized the surgical trauma, reduced the chair time, and improved patient acceptance.[49]

Obviously, the aid of surgical telescopes (loupes), and/or of surgical microscopes is mandatory in order to perform adequately these procedures,[50,51] which, in turn, requires a certain learning curve to enable the clinician to correctly perform these procedures.

Another critical factor for optimizing the clinical outcomes is the suturing technique. It has been demonstrated that following flap surgery, the mean tensile strength was markedly weaker at the dentine-flap interface when compared to the bone-flap interface. After 1 week, the value measured 1.82 N for the former and 5.08 N for the latter,[52] thus confirming the need to stabilize the periodontal flaps at the soft/hard tissue interfaces by means of appropriate suturing techniques. Furthermore, it needs to be kept in mind, that wound healing following periodontal flap surgery at hard, nonshedding surfaces is a more complex process than wound healing in most other sites of the oral cavity, which, in turn, emphasizes the need for careful tissue management and flap adaptation and suturing.[22] A number of studies have clearly shown the need to control closing forces at the wound margins to minimize tissue trauma. It has been also suggested that finer suture diameters (i.e., 6–0, 7–0) bear more advantages compared to thicker sutures since they rather lead to thread breakage than to tissue tear and breakage.[53]

Since the primary objective of suturing is to position and secure the margins of the surgical wound until the wound has healed or has enough strength to withstand physiological demands, stable anchorage points need to be used in order to enable adequate stability for a sufficient time period needed for early wound healing (i.e., 1–2 weeks postoperatively).[54]

Among the most commonly used sutures in regenerative periodontal surgery, are the sling or suspensory sutures, various types of mattress sutures or combinations thereof.

Taken together, it can be recommended that regenerative periodontal surgery should nowadays be performed with the help of an adequate magnification and microsurgical instruments while flap closure should be achieved by means of sling or suspensory sutures, mattress sutures or combinations thereof using finer suture diameters (i.e., 6–0, 7–0).

Operator skills and training

Based on earlier observations of a center effect in multicenter trials evaluating regenerative procedures (reviewed in Cortellini & Tonetti[30]), the operator/surgeon with his/her surgical skills has received much attention as an important factor influencing the regenerative outcomes.

In fact, the current EFP S3-Level Clinical Practice Guideline[1] states that surgical treatment is effective but frequently complex and recommends, that it is provided by dentists with additional specific training or by specialists in referral centers.

Indeed, advanced periodontal surgery (regenerative and furcation management) is beyond the scope and competence of education in general dental practice,[55] whereas postgraduate periodontal education, on the other hand, is specifically designed to provide competence and proficiency towards the solution of such complex problems.[1,56,57]

Thus, performing regenerative periodontal procedures without having received additional training could be viewed as treatment error.

2.3.2 | Selection of biomaterials/regenerative technique

With regard to the adequate choice of regenerative biomaterials for promoting healing of residual deep pockets associated with intrabony defects, the current EFP S3-Level Clinical Practice Guideline[1] states: "In regenerative therapy, we recommend the use of either barrier membranes or enamel matrix derivative with or without the addition of bone-derived grafts." With regard to the adequate choice of regenerative biomaterials for the regenerative treatment of residual deep pockets associated with Class II mandibular and maxillary buccal furcation involvement, it is stated: "We recommend treating molars with residual pockets associated with mandibular and maxillary buccal Class II furcation involvement with periodontal regenerative therapy using enamel matrix derivative alone or bone-derived graft with or without resorbable membranes."

It is further stated: "Clinicians should select a specific biomaterial to be used to promote regeneration at intrabony defects (or Class II furcation involvements) based on satisfaction of all of the following criteria[58]: (a) availability of solid preclinical research identifying plausible mechanism(s) of action leading to periodontal regeneration; (b) human histological evidence of regeneration in the specific application; and (c) evidence of efficacy in applicable, high-quality randomized controlled clinical trials. While there are biomaterials that satisfy all these criteria, it must be understood that many biomaterials do not meet them in spite of being CE ("Conformité Européene") marked or Food and Drug Administration (FDA)-approved/cleared".

Thus, employing a biomaterial for regeneration that does not satisfy all of the above criteria could be viewed as a treatment error.

Apart from the recommendations given above, the individual selection of a regenerative biomaterial/technology for a given situation should be based on the surgical access performed as well as on the defect configuration, and corresponding decision-making algorithms have been proposed.[5,30]

2.4 | Postoperative care, maintenance

Postsurgical and early home-care protocols after regenerative periodontal surgery have been proposed and are derived from the experience collected in clinical trials. Empirical protocols often include prophylactic antibiotics and chlorhexidine mouth rinses to avoid postoperative infections. Moreover, patients are usually advised to abstain from mechanical plaque removal in the surgical area for up to 6 weeks and to attend weekly recall visits to allow for monitoring of the healing process. Later, patients enter a 3 months-recall system for supportive care. Any invasive procedures in the treated area should be avoided for up to 1 year to optimize healing outcomes.

Typical postoperative complications after regenerative surgical procedures may include among others pain, wound dehiscence, papilla necrosis, abscess formation, and membrane exposure (Figure 8).

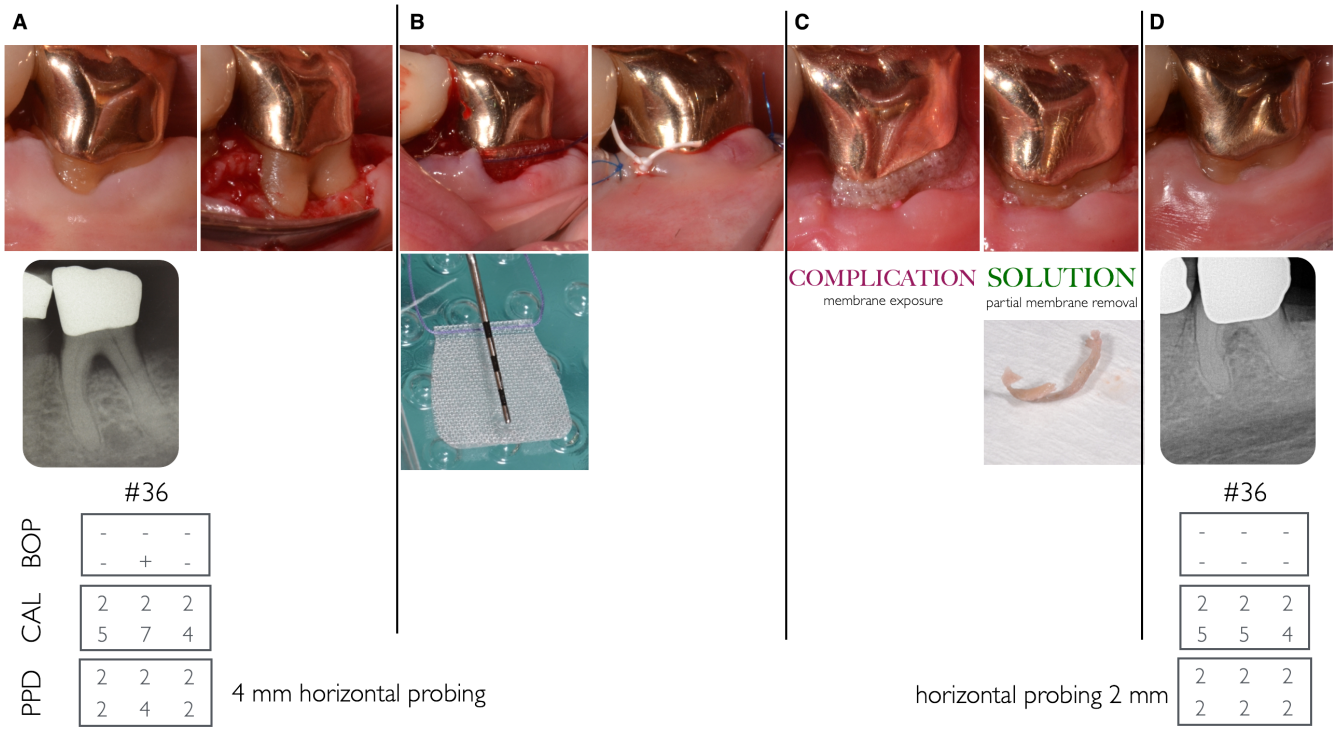

FIGURE 8 Healing complication: membrane exposure. Tooth #36 with a buccal class II furcation in a 60-year-old healthy patient. Periodontal measurements: pocket probing depth mesial and distal: 2 mm, horizontal furcation probing: 4 mm, gingival recession: 3 mm. Radiograph of tooth #36 with visible furcation defect, adjacent bone level was slightly above of the roof of the furcation (A). Flap elevation: intrasulcular incision and mucoperiosteal flap elevation, papillae de-epithelialized, periosteal splitting in the vestibule, instrumentation of the root surface. Placement of a resorbable barrier membrane, fixation of the barrier with integrated sling sutures and coronally positioned flap, fixed with sling and interrupted sutures (B), exposure of barrier membrane 3 weeks after surgery and careful removal of visible part of the matrix with a scalpel (C). 3 years after the intervention the long-term result was not compromised: horizontal and vertical probing depths: 2 mm, recession: 3 mm, radiograph shows complete radiographic bone fill in the furcation area (D).

Systemic antibiotics given perioperatively or postoperatively are often prescribed with the objective to prevent postoperative infections and to reduce postsurgical complications during the early healing period. Interestingly, their effect has been rather underresearched compared with the use of systemic antibiotics during step 2 of periodontal therapy.[1] Thus, in the reality of clinical practice antibiotics are often empirically prescribed in conjunction with regenerative surgery with no clear evidence to support it. In a recent systematic review[59] data from 2 systematic reviews[3,4] including 105 randomized clinical trials were retrieved to explore the potential benefit of the use of systemic antibiotics (AB). At the same time, the frequencies of adverse events/postoperative infections were assessed. Interestingly there was no direct and only weak indirect evidence for a benefit in intrabony defects and no evidence for a benefit in furcations. No clear differences in adverse events/complications were detected between AB and non-AB groups. In the few studies on intrabony defects that had performed a direct comparison, apart from erythema and swelling, no severe postoperative complications such as suppuration, sloughing, perforation of the flap, and postoperative pain were reported in either of the groups. In studies on intrabony defects, included in the single-arm meta-regression only four specifically reported adverse events or postoperative infections following the use of membranes. A higher frequency of postoperative adverse events was reported after regenerative treatment of furcations, mostly related to the use of nonresorbable membranes, however, both in treatment arms with or without a postoperative antibiotic protocol.

Based on these findings, the lack of systemic antibiotic prophylaxis in conjunction with regenerative periodontal surgery does not seem to increase the frequency of postoperative complications and should not be viewed as a treatment error.

Notably, in spite of an intervention with systemic antibiotics (Amoxicillin and Metronidazole, as usually prescribed in periodontal infections) a postoperative complication (Figure 9) could not be resolved due to the presence of multi-resistant *Enterobacter* species.[60]

It has been demonstrated that regenerative therapy can be even applied to hopeless teeth and has the potential to change their prognosis; it was concluded to be a suitable alternative to extraction of severely compromised teeth with intrabony defects to or beyond the root apex.[31] After 10 years and under a strict periodontal 3-monthly supportive care regimen and yearly examinations the same authors reported a survival rate of 88% in these regeneratively treated severely compromised teeth. The complication-free survival here was 6.7–9.1 years.[61] Here, late complications were defined as clinical attachment loss, deepening of pockets, or radiographic bone loss of 2 mm or more compared with

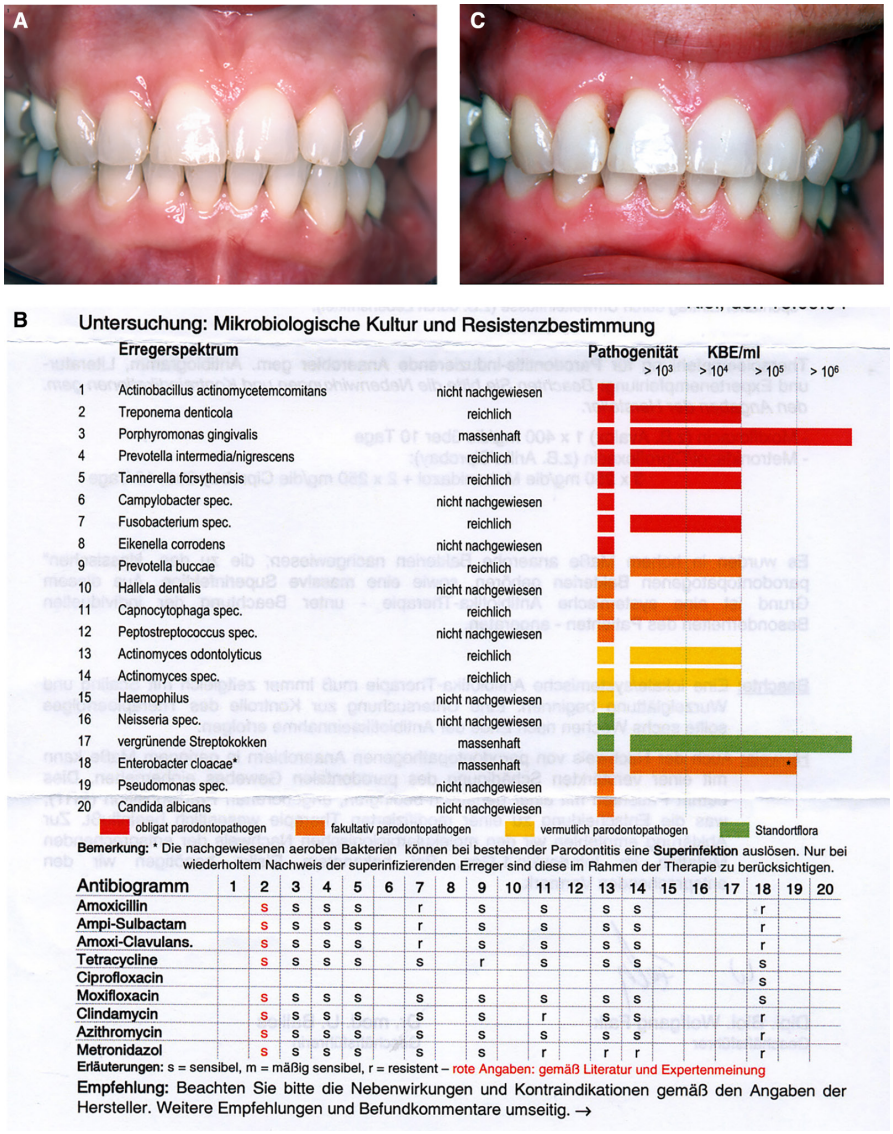

FIGURE 9 Atypical infectious and aesthetic complication. Loss of papilla between tooth #12 and #11 due to an atypical postoperative infection including *Enterobacter* species. Preoperative radiographic situation and periodontal probings around teeth #12 and #11 taken after step 1 and 2 periodontal therapy (A). The patient was 44 years old, a previous smoker and otherwise healthy. After nonsurgical periodontal therapy, a simplified papilla preservation flap in combination with EMD (Emdogain®, Straumann, Basel, Switzerland) was chosen for regeneration of an intrabony defect located at the mesial aspect of tooth #12. After 10 days the patient presented with a postoperative swelling and suppuration. In spite of an intervention with combined systemic antibiotics (Amoxicillin and Metronidazole) the situation had not improved 3 days later. Microbiological diagnostics revealed an atypical spectrum of periodontal bacteria including multi-resistant *Enterobacter* species[60] (B). After six months and regular maintenance visits with application of local antiseptics, the clinical situation slowly improved, however, with permanent loss of the papilla and aesthetic impairment (C).

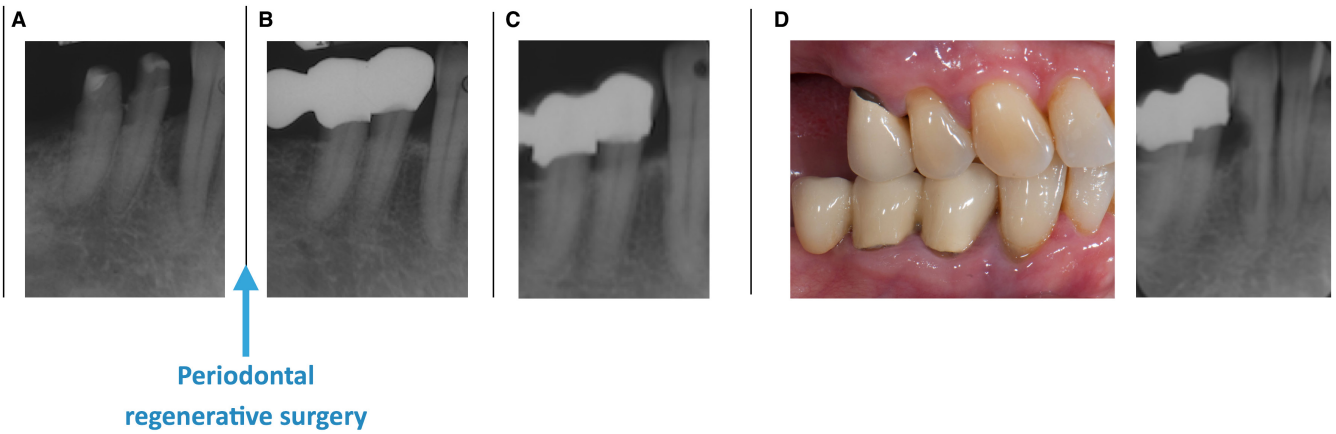

FIGURE 10 Late complication: root resorption. Ten years after periodontal regeneration of an extensive vertical defect in a 68-year-old female medically compromised patient with osteoporosis (medication: Fosamax bisphosphonate). Advanced periodontitis with deep vertical defect on the distal aspect of tooth #43 (A). After consulting with her osteologist regenerative surgery was performed supplemented with perioperative systemic antibiotics using EMD (Emdogain®, Straumann) and deproteinized bovine bone mineral (BioOss®, Geistlich). Irregular maintenance visits, radiographs before surgery (A), After 2 years (B) and 7 years (C) considerable radiographic bone gain on the distal aspect of tooth #43; after 10 years (D) the patient came back complaining about a mobile tooth #43. Clinical findings showed pus on tooth #43, mobility grade 2, and pocket probing depth of 10 mm on the distal aspect. The radiograph showed an advanced external root resorption.

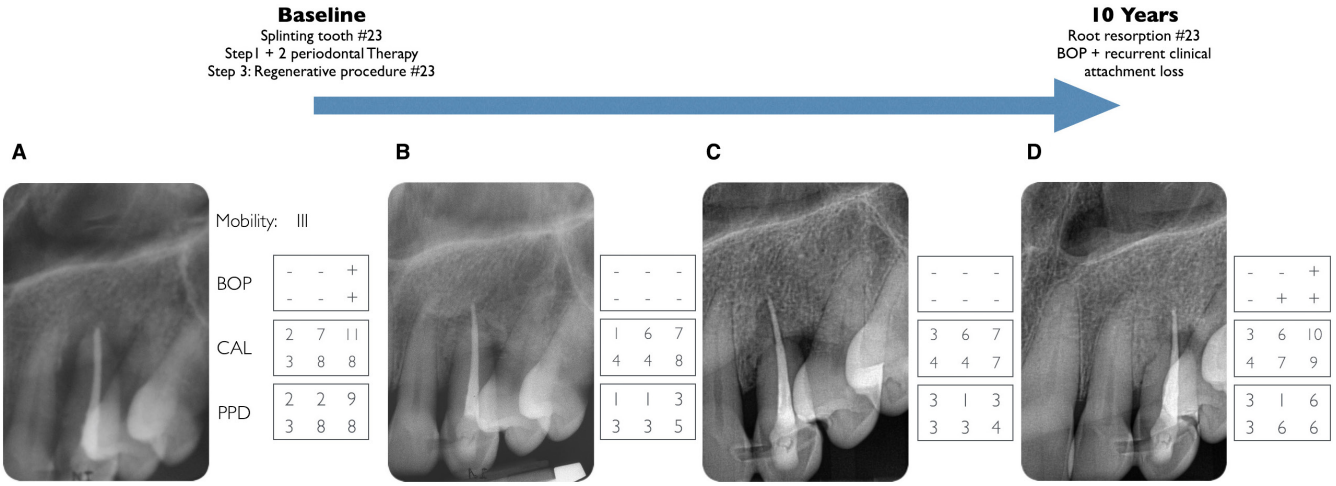

FIGURE 11 Late complication: root resorption. Ten years after regeneration of a large intrabony defect. Radiographic situation and periodontal probings of a 61-year-old patient complaining about an upper left loose canine #23 with mobility 3, and a recession RT3 (A). The reason for referral was an increasing mobility of tooth #23. She was horrified about losing her tooth and reported that her general dentist had just recently performed root canal therapy. Since then, mobility had not improved. With the diagnosis periodontitis stage IV and an endo-perio-lesion of unclear origin tooth #23 was splinted accompanied by step 1 and 2 of periodontal therapy. Step 3 included a regenerative procedure with a modified papilla preservation flap design. After flap elevation the large defect extended around the root tip but was mainly surrounded by bony walls. After thorough debridement the root surface was conditioned with EMD (Emdogain®, Straumann), and the defect was filled with deproteinized bovine bone mineral (BioOss-Collagen®, Geistlich). A connective tissue (CTG) graft was combined with a soft tissue substitute (Mucograft®, Geistlich) for improved stability and was placed on to the buccal aspect of the tooth according to the "connective tissue graft wall technique".[62] Healing was uneventful, monofilic sutures (6–0) were removed after 14 days. The situation remained stable up to 6 years (B) and 8 years (C). At her 10-year maintenance recall the patient complained about pain on probing of tooth #23. Radiographic evidence of root resorption after 10 years was accompanied by clinical attachment loss and bleeding of probing (D).

the 1-year outcome, loss of tooth vitality, or onset of caries. Other late complications such as root resorption may also occur. Examples are presented in Figures 10 and 11.

3 | CONCLUSIONS

Regenerative periodontal surgical procedures are an important component of the treatment of advanced periodontitis. They can significantly improve the periodontal condition and long-term prognosis of teeth with intrabony defects or class II furcations. However, they require a careful selection of patients and teeth/defects by meticulous diagnostics, an intensive training of the necessary (micro-)surgical techniques and should only be carried out in highly motivated patients with good adherence to regular supportive care. By proper planning and execution of treatment, complications can be minimized and treatment errors can be avoided.

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CONFLICT OF INTEREST STATEMENT

The authors do not declare any conflict of interest related to this manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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