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Factors influencing periodontal regeneration

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One statement holds true for all meta-analyses of regenerative periodontal therapy: the results show a marked heterogeneity, i.e. the results of regenerative therapy vary widely. What is the reason for this? Is it left to chance whether flap surgery with regenerative procedures, such as guided tissue regeneration (GTR) or enamel matrix proteins (EMP), results in improved attachment gain or osseous filling? Or are there factors that influence therapeutic success? One thing is clear: before planning regenerative procedures, anti-infectious therapy should be completed. Patients should practice proper personal oral hygiene and, other than the defects that are to be regenerated, residual pockets should be absent. Other factors influencing the success of regenerative therapy in bony pockets and class II furcation defects are smoking, defect depth and breadth, availability of soft tissue for flap formation, position of the furcation fornix in relation to approximal bone, and tooth mobility.

■ Introduction

Regenerative periodontal therapy yields better clinical and radiological results in bony pockets and class II furcation defects than access flap surgery. When comparing the results of different clinical studies in the course of meta-analyses, however, there is a high degree of heterogeneity, i.e. there are marked differences between the results of individual studies[1-3].

With respect to regenerative therapy of bony pockets, results range from 'no difference compared with access flap'[4] to 'regenerative therapy strongly superior'[3-6].

How can this heterogeneity be explained? Beyond the therapeutic procedure (access flap/regenerative therapy) there is a wide range of factors for which we either know or suspect that they influence periodontal wound healing in a general way (e.g. age, smoking, concurrent medication, post-operative care, supportive periodontal therapy, oral hygiene, defect morphology). However, which are the factors that influence the short-term and long-term success of regenerative periodontal therapy?

■ Patient characteristics (Table 1)

■ Smoking

Smoking is the most important external risk factor for periodontitis (see for example[7,8]), and it is a known fact that smoking generally has a detrimental effect on the results of periodontal therapy (see for example[9,10]). Many studies provide evidence of the detrimental effect of smoking on the results of regenerative therapy[11-18].

■ Age

The assumption that the regenerative potential of periodontal tissues decreases with increasing age seems plausible. However, until recently age could only be shown to be related to reduced osseous filling after guided tissue regeneration (GTR) of bony pockets[13]. Clinical results of class II furcation defects could not be correlated to the patients' age[19].

■ Interleukin-1 polymorphism

Interleukin-1 (IL1) plays an important role in the inflammation reaction of periodontal tissues. One interleukin-1 polymorphism complex was associated with increased risk of periodontitis[20]. De Sanctis and Zucchelli[21] could find no difference in attachment gains between patients with and without IL-1 polymorphism one year after regenerative therapy of bony pockets. Four years after therapy, however, the attachment gains in IL-1 positive patients proved less stable[21]. To date, other studies have not confirmed this effect of IL-1 polymorphism on long-term results[17,22,23].

■ Persistent infection

It can be demonstrated that poor oral hygiene and persistent infection with *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans* has a detrimental effect on healing of class II furcation defects. Patients who continued to have generalised, persistent, pathologically deepened pockets showed inferior results after GTR of infra-alveolar defects than those who after anti-infectious therapy had no pockets ≥ 5 mm[24]. Persistent pockets are filled with periodontal pathogens, which in turn can populate the regenerative site and thereby destroy the prospects of regeneration. Therefore anti-infectious therapy should be completed before considering regenerative measures.

■ Defect morphology

■ Bony pockets (Table 2)

There are indications that two- and three-walled bony pockets respond better to regenerative therapy than single-wall defects[13]. On the other hand, several studies have demonstrated that the extent of vertical attachment gain[25,26] or osseous filling[14,16,25] correlates with the total corono-apical extent of the bony pockets, including the single-wall component. In other words, the deeper the bony pocket, the greater attachment gains and the better osseous filling may be expected (Figs 1 and 2a). Infra-alveolar

Table 1 Patient characteristics that influence the results of regenerative therapy

Positively	Negatively
Effective personal oral hygiene	Smoking
	Persistent infection with *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*
	(Interleukin-1 polymorphism)

Table 2 Defect characteristics that influence the results of regenerative therapy in bony pockets

Positively	Negatively
Deep bony pockets (> 3 mm)	Shallow bony pockets (≤ 3 mm)
Narrow radiological defect angle	Wide radiological defect angle
High values of probing depth before surgery	Increased tooth mobility

Fig 1a Clinical measurement: probing depth 8 mm; vertical attachment loss 10 mm; wide interdental papilla; no furcation involvement.

Fig 1b Intraoral X-ray indicating the presence of a primarily single-wall defect with a lateral wall toward the neighbouring second premolar; wide defect angle.

Fig 1c Intra-operative view: infra-alveolar component 5 mm; two- and three-wall component 2 to 3 mm.

Figs 1a to 1c Bone pocket distal of the teeth 24.

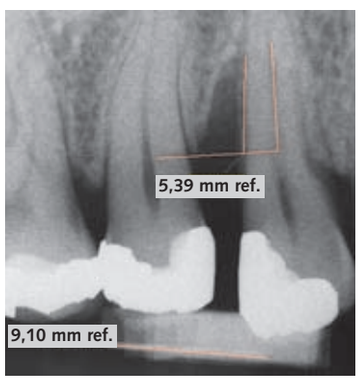


Fig 2a Deep infra-alveolar component (> 4 mm).

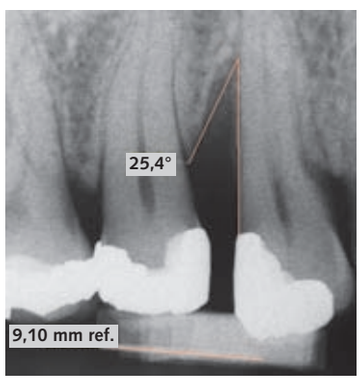


Fig 2b Narrow defect (< 27°).

Figs 2a and 2b Radiological defect characteristics for guided tissue regeneration therapy in bony pockets: tooth 14. Favourable conditions for regenerative therapy.

defects of less than 3 to 4 mm depth tend to lose rather than gain bone substance when subjected to regenerative measures[14,16].

Another aspect of infra-alveolar defects is the defect angle. Narrow defects allow for better gains of attachment[25,27] and bone substance[14,16,25] than wide defects (Fig 2b). Varying threshold values were used to define narrow defects in different studies: Klein et al[14], < 26°; Eickholz et al[16], < 37°; Tsitoura et al[27], ≤ 2°. The shallower and the wider a bony pocket is, the more it resembles horizontal bone resorption, which cannot be influenced by regenerative therapy. It appears, however, that the defect angle is a function of defect depth, as defect width is limited by the width of the interdental space and the action radius of the bacterial plaque[28].

When applying regenerative techniques, the aim is always to cover perfectly the defect with the GTR barrier or the enamel matrix protein (EMP). In some cases, barriers create space coronal of the osseous walls[5]. In such cases, the flap must be shifted in a coronal direction in order to achieve complete wound closure. In those cases in which advanced attachment losses are combined with deep pockets, there is sufficient soft tissue available for coronal shifting at the respective site. Deeper pockets at sites with infra-alveolar defects therefore correlate with better attachment gains[16,29-31].

The fact that a tooth has been subjected to root canal treatment does not worsen conditions for applying regenerative procedures[29]. Increased preoperative mobility of a tooth does, however, have a detrimental effect on the results of regenerative therapy[12]. In situations with increased tooth mobility, neither the blood clot that forms in the defect nor the barrier can be sufficiently stabilised. In these cases,

there is a high risk of the connection between the blood clot and the root surface rupturing, which leads to apical growth of the epithelium towards the bottom of the defect cavity.

Class II furcation defects (Table 3)

While GTR therapy in class II furcation defects[32] of maxillary and mandibular molars allows for better horizontal defect filling (i.e. horizontal attachment and/or bone substance gain) than access flap surgery[2,3], this advantage of regenerative versus standard therapy cannot be observed in class II defects with furcation involvement in premolars[33]. No differences can be observed between results achieved after GTR therapy of first and second mandibular molars[15,19]. The degree of furcation involvement is an important factor influencing the main objectives of regenerative furcation therapy, namely attachment and/or bone substance gain. On the one hand, shallow furcation defects (class I) have an equally good prognosis as molars without furcation involvement[34] and hence do not profit from regenerative therapy. On the other hand, reliable closure of open furcations (class III) has not yet been successfully achieved[2,13,35]. It follows that only class II furcation defects are a suitable indication for regenerative therapy.

Apart from the degree of furcation involvement, furcation location is another factor influencing the therapy result: class II furcation defects in mandibular molars and buccal furcations in maxillary molars respond better to GTR therapy than approximal furcation defects[2,35].

As with bony pockets, high pre-operative probing depth values in the area of the furcation defect have a beneficial influence on the results of regenerative therapy[19,36]. Deep pockets signal a smaller degree of recession and at the same time marked vertical attachment loss and thus sufficient soft tissue to achieve complete covering of the defect or the barrier or EMP. Other authors have, however, reported a significant negative correlation between pre-operative probing depths and the number of complete closures of furcation defects achieved[15]. These discrepancies may possibly be explained in terms of differences in defect morphology. Deep pockets with or without osseous wall may be present in the apical region of the furcation defect. The larger the osseous furcation aperture, the worse the clinical results expected[15,36]. Wide furcations respond less well to regenerative therapy than narrow furcations[15,36]. The wider the furcation aperture, the more difficult it is to close the defect (Fig 3a). Complete filling of the defect is also less likely in deep class II furcation defects (≥ 5 mm)[15]. A long root trunk is another factor that negatively influences therapy results when furcations are involved: with long root trunks, an advanced stage of bone resorption is necessary to cause furcations to be affected at all. A molar tooth that presents such conditions is generally badly damaged in its periodontium and does not respond well to regenerative therapy (Fig 3b). If the furcation fornix is situated apical of the approximal bone level ('keyhole defect'), more horizontal attachment gain is to be expected than in cases where the furcation fornix is situated coronal of the approximal alveolar crest. On condition that there is bone substance on both sides of the tooth coronal of the furcation fornix, covering and stabilising of the GTR membrane can be achieved using a coronally positioned flap. Furthermore, the surface of the periodontal space from which the cells that are to infiltrate the blood clot inside the defect emerge is larger under such conditions than in cases where the fornix is situated coronal of the alveolar crest (Fig 3c)[15,36].

Table 3 Defect characteristics that influence the results of regenerative therapy in class II furcation defects

Positively	Negatively
Furcation fornix situated apical of approximal bone level	Long root trunk
Buccal and lingual position	Interproximal position
High values of probing depth before surgery	Deep class II furcation defect (≥ 5 mm)
	Wide furcation aperture
	High furcation aperture

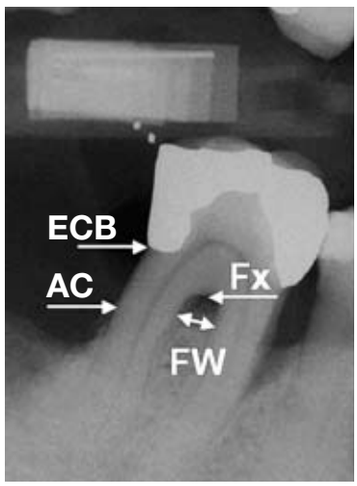


Fig 3a ECB, enamel–cementum border (restoration border); AC, alveolar crest; Fx, furcation fornix; FW, furcation width.

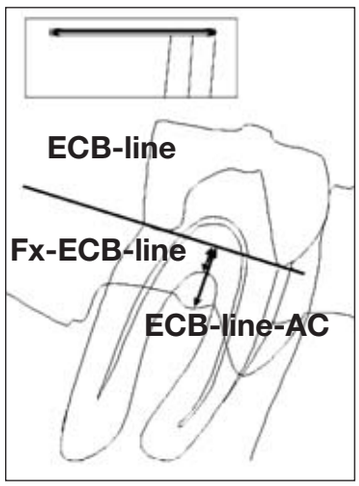


Fig 3b ECB line, line connecting mesial and distal enamel–cementum border (ECB); distance to Fx-ECB line, length of root trunk. ECB-line-AC, distance from ECB line to alveolar crest (AC).

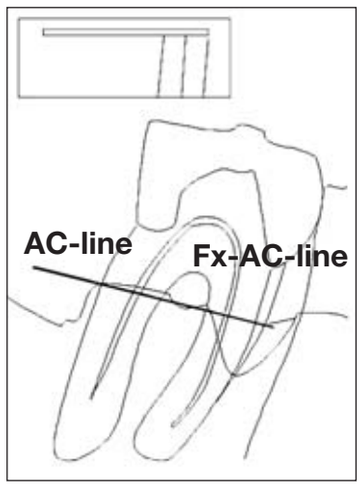


Fig 3c AC-Line, line connecting mesial and distal alveolar crest (AC); distance to Fx-AC line, fornix situated coronal of approximal AC (unfavourable condition for application of GTR).

Fig 3a to c Radiological defect characteristics for guided tissue regeneration therapy in class II furcation defects: tooth 46 (Horwitz et al[36]).

■ Surgical procedure and post-operative complications (Table 4)

■ The influence of the surgeon

In some, but not in all multi-centre studies, a distinct centre effect could be observed even when taking into account patient and defect characteristics[27,29-31]. This may be interpreted in terms of the influence of the surgeon on short-term results of regenerative therapy.

■ Membrane material

There are a large variety of materials for regenerative therapy available on the market. With non-resorbent membranes, the most experience and most extensive data compiled has been for expanded polytetrafluoroethylene (ePTFE). Apart from this, there are a large variety of biological and synthetic biodegradable barrier materials that make it possible to do without the second surgical intervention necessary to remove non-resorbent membranes[37]. Finally, there are also EMP that enable periodontal regeneration[38]. In most studies, no difference was found with respect to the clinical and radiological results after application of non-resorbent and biodegradable membranes respectively[39-43]. Biodegradable barriers for bony pockets and class II furcation defects generally work just as well as non-resorbent ePTFE membranes[3]. Regenerative therapy using EMP also yields better results in bony pockets than standard flap surgery[38]. When comparing clinical results after regenerative therapy with membranes and EMP respectively, no significant or clinically relevant differences can be found for

Positively	Negatively
Complete membrane coverage of the defect	Wound dehiscence, membrane/defect exposure
Regular supportive periodontal therapy (SPT) carried out by a specialised dentist or periodontologist	
Skilled surgeon	

Table 4 Therapeutic procedures and post-operative complications that influence the results of regenerative therapy

infra-alveolar defects[38]. Only one paper on class II furcation defects has been presented to date, which came to similar conclusions with respect to EMP and membranes[44]. The frequency of post-operative complications (e.g. wound dehiscence) is lower after application of EMP, however[38,45].

Post- and peri-operative medication

In most clinical studies on regenerative therapy, post- or peri-operative antibiotic regimes are used, e.g. 250 mg tetracyclin four times daily for one week[5,46], 1.5 g amoxicillin once daily for one week[26], 200 mg doxycyclin once daily for one week[12,29-31], 1 g amoxicillin with clavulan acid once daily for 8 days[21], a single dose of 3 g amoxicillin 30 to 60 minutes before surgery[47]. However, few studies have investigated the effect of antibiotics that were administered in addition to regenerative therapy: ornidazol for 10 days starting two weeks after surgery[48]. Some studies did not yield better clinical results after GTR with antibiotics than after GTR without antibiotics: propicillin[49]; metronidazole and ciprofloxacin[50]; vibramycin, amoxicillin or metronidazole[51]; amoxicillin and metronidazole[52]. It appears that additional administration of antibiotics does not improve regenerative therapy results.

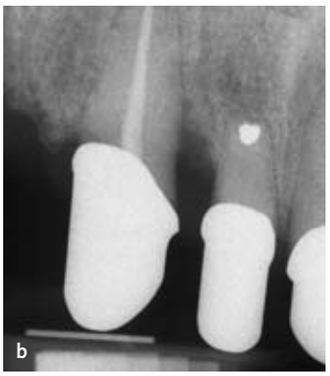
Use of antiphlogistic agents (e.g. cyclo-oxygenase-2 inhibitors) does not improve regenerative therapy results either[53].

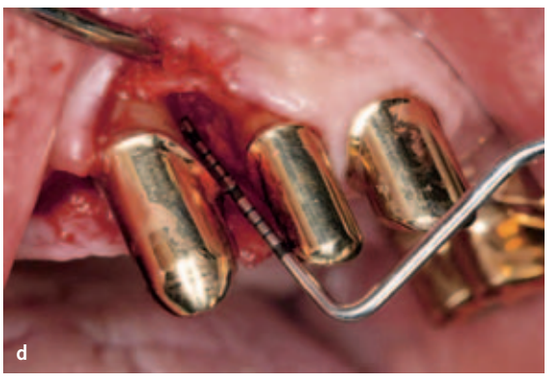
Wound dehiscence and membrane exposure

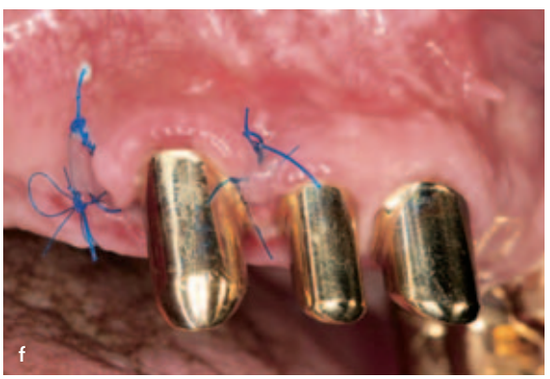
Post-operative wound dehiscence and membrane exposure is often reported after GTR therapy, especially of approximal bony pockets (Fig 4)[47]. Interproximal tissue maintenance (ITM)[54], a flap technique designed to conserve approximal tissue, as well as the modified (Fig 5)[46,55] and the simplified papilla preservation flap[56] were developed in order to achieve complete wound closure[57]. Primary wound closure could be achieved in 14 out of 15 cases (93%) after application of the modified papilla preservation flap technique for GTR therapy using titanium-reinforced ePTFE membranes. Two membrane exposures occurred 3 weeks after surgery and one more 4 weeks after surgery. When the membranes were removed (6 weeks after surgery), 11 defects were still completely covered (73%). However, a sufficiently wide interdental papilla is required for successfully applying this technique[46]. It reaches its limits in narrow interdental spaces and with molars. This is why another modification of the papilla preservation technique was developed: the simplified papilla preservation flap technique. After using the simplified papilla preservation flap for GTR therapy with biodegradable membranes, primary wound closure was achieved in all 18 defects (100%). Three membrane exposures occurred 1 week after surgery and three more 2 weeks after surgery. Six weeks after surgery, 12 defects were still completely covered (66.6%)[56].

Fig 4 Flap dehiscence and exposure of an ePTFE membrane 4 weeks after treatment of an infra-alveolar defect distal of the tooth with GTR therapy[23].

Some authors have noted poorer attachment gains with membrane exposure one year after GTR therapy using ePTFE barriers[21], while others could not report such findings after application of non-resorbent and biodegradable membranes respectively[16]. The fact that deep pockets before surgery, i.e. sufficient availability of soft tissue for defect coverage, enhances the chance of achieving better results after regenerative therapy of bony pockets as well as of class II furcation defects, indicates that, at least initially, complete wound closure is a prerequisite for optimal results. A meta-analysis concerning the effect of membrane exposure on wound healing included five studies on class II furcation defects (101 defects) and five studies on bony pockets (309 defects).







Figs 5a to 5h Modified papilla preservation flap mesial of tooth 13.

Fig 5a Situation prior to surgical intervention: probing depth 8 mm; attachment loss 7 mm; interdental papilla ≥ 2 mm.

Fig 5b Pre-operative X-ray: mesial bony pocket.

Fig 5c Circular intracrevicular incision in the vicinity of teeth 13 and 12; semilunar interdental vestibular incision.

Fig 5d After mobilising mucoperiostal flap: mainly three-walled bony pocket with infraalveolar component > 4 mm.

Fig 5e Vertical mattress sutures and single button sutures (monofile propylene threads 4/0 and 6/0 respectively).

Fig 5f One week after surgery.

Fig 5g Two weeks after surgery.

Fig 5h Six months after surgery.

Poorer horizontal and vertical attachment gains respectively were confirmed for both types of defect upon membrane exposure[58].

■ Supportive periodontal therapy

It has often been demonstrated and is widely accepted that the results of periodontal therapy can only be kept stable if the patients take part in supportive periodontal therapy (SPT) on a regular basis[59,60]. SPT is also of great significance for the stability of regenerated periodontal tissues[11]. There are indications that this maintenance therapy after periodontal regeneration should be carried out by a specialist or specialised dentist rather than under the conditions of a general dental practice. Failure to carry out SPT is, together with smoking, a strong risk factor for loss of attachment and tooth loss after regenerative therapy[17]. It is therefore justified to say that SPT is not everything, but without SPT everything that has been achieved is reduced to nothing.

■ Conclusions

After 20 years of clinical research in the subject area of regenerative periodontal therapy, a number of prognostic factors have been identified and confirmed. Although we probably do not (as yet) know all factors that influence periodontal therapy in general and regenerative therapy in particular, the knowledge available at present does enable the dental clinician to select the therapeutic procedure with the best chance of improving the periodontal situation of badly damaged teeth. In other words, the dentist has a variety of valid criteria at his disposal in order to select patients and defects for successful regeneration. When all criteria, including the surgeon's skill in performing regenerative measures, are optimal, the best results after regenerative therapy can be expected. If most of the determining factors for regenerative therapy are favourable (e.g. deep bony pockets, no increased tooth mobility, no persistent infection), a single less favourable factor (e.g. occasional smoking) can be tolerated, and good results can still be achieved with regenerative therapy. Whether or not to carry out regenerative therapy of a defect in a specific patient is thus a multi-factorial decision that should take into consideration the cost of the intervention in relation to the expected benefit. When, on the basis of many prognostic factors, less favourable results after regenerative therapy are to be expected, other therapy options (e.g. resective therapy) should be considered.

Regenerative periodontal therapy has broadened the range of periodontal treatment options. It is, nevertheless, certainly no magic wand to miraculously solve all periodontal problems without effort.

■ References

1. Needleman IG, Worthington HV, Giedrys-Leeper E, Tucker RJ. Guided tissue regeneration for periodontal infra-bony defects (Cochrane Review). The Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD001724. DOI:10.1002/14651858.CD001724.
2. Jepsen S, Eberhard J, Herrera D, Needleman I. A systematic review of guided tissue regeneration for periodontal furcation defects. What is the effect of guided tissue regeneration compared with surgical debridement in the treatment of furcation defects? J Clin Periodontol 2002;29(Suppl. 3): 103–116.
3. Murphy KG, Gunsolley JC. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. Ann Periodontol 2003;8:266–302.
4. Ratka-Krüger P, Neukranz E, Raetzke P. Guided tissue regeneration procedure with bioabsorbable membranes versus conventional flap surgery in treatment of infrabony defects. J Clin Periodontol 2000;27:120–127.
5. Cortellini P, Pini Prato G, Tonetti MS. Periodontal regeneration of human intrabony defects with titanium reinforced membranes. A controlled clinical study. J Periodontol 1995;66:797–803.
6. Cortellini P, Pini Prato GP, Tonetti MS. Periodontal regeneration of human infrabony defects with bioresorbable membranes. A controlled clinical trial. J Periodontol 1996;67: 217–223.
7. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, Norderyd OM, Genco RJ. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol 1994;65:260–267.
8. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: Findings from NHANES III. J Periodontol 2000;71:743–751.
9. Eickholz P, Kim T-S, Schacher B, Bürklin T, Renggli HH, Schaecken MT, Holle R, Kübler A, Ratka-Krüger P. Non-surgical periodontal therapy with adjunctive topical doxycycline: A double blind randomized controlled multicenter study. I. Study design and clinical results. J Clin Periodontol 2002;29:108–117.
10. Trombelli L, Cho K-S, Kim C-K, Scapoli C, Scabbia A. Impaired healing response of periodontal furcation defects following flap debridement surgery in smokers. A controlled clinical trial. J Clin Periodontol 2003;30:81–87.
11. Cortellini P, Pini Prato GP, Tonetti MS. Long-term stability of clinical attachment following guided tissue regeneration and conventional therapy. J Clin Periodontol 1996;23:106–111.

12. Cortellini P, Tonetti MS, Lang NP, Suvan JE, Zucchelli G, Vangsted T, Silvestri M, Rossi R, McClain P, Fonzar A, Dubravec D, Adriaens P. The simplified papilla preservation flap in the regenerative treatment of deep intrabony defects: Clinical outcomes and postoperative morbidity. J Periodontol 2001;72:1702–1712.
13. Eickholz P, Hausmann E. Evidence for healing of interproximal intrabony defects after conventional and regenerative therapy: Digital radiography and clinical measurements. J Periodont Res 1998;33:156–165.
14. Klein F, Kim TS, Hassfeld S, Staehle HJ, Reitmeir P, Holle R, Eickholz P. Radiographic defect depth and width for prognosis and description of periodontal healing of infrabony defects. J Periodontol 2001;72:1639–1646.
15. Bowers GM, Schallhorn RG, McClain PK, Morrison GM, Morgan R, Reynolds MA. Factors influencing the outcome of regenerative therapy in mandibular class II furcations: Part I. J Periodontol 2003;74:1255–1268.
16. Eickholz P, Hörr T, Klein F, Hassfeld S, Kim T-S. Radiographic parameters for prognosis of periodontal healing of infrabony defects: Two different definitions of defect depth. J Periodontol 2004;75:399–407.
17. Cortellini P, Tonetti MS. Long-term tooth survival following regenerative treatment of intrabony defects. J Periodontol 2004;75:672–678.
18. Stavropoulos A, Mardas N, Herero F, Karring T. Smoking affects the outcome of guided tissue regeneration with bioabsorbable membranes: A retrospective analysis of intrabony defects. J Clin Periodontol 2004;31:945–950.
19. Machtei EE, Cho MI, Dunford R, Norderyd J, Zambon JJ, Genco RJ. Clinical, microbiological, and histological factors which influence the success of regenerative periodontal therapy. J Periodontol 1994;65:154-–161.
20. Kornman KS, Crane A, Wang H-Y, di Govine FS, Newman MG, Pirk FW, Wilson TG jr, Higginbottom FL, Duff GW. The interleukin-1 genotype as a severity factor in adult periodontal disease. J Clin Periodontol 1997;24:72–77.
21. De Sanctis M, Zucchelli G. Interleukin-1 gene polymorphisms and long-term stability following guided tissue regeneration therapy. J Periodontol 2000;71:606–613.
22. Christgau M, Aslanidis C, Felden A, Hiller KA, Schmitz G, Schmalz G. Influence of interleukin-1 gene polymorphism on periodontal regeneration in intrabony defects. J Periodont Res 2003;38:20–27.
23. Eickholz P, Krigar D-M, Kim T-S, Reitmeir P, Rawlinson A. Stability of clinical and radiographic results after guided tissue regeneration in infrabony defects. J Periodontol 2007; 78:37–46.
24. Nowzari H, MacDonald ES, Flynn J, London RM, Morrison JL, Slots J. The dynamics of microbial colonization of barrier membranes for guided tissue regeneration. J Periodontol 1996;67:694–702.
25. Tonetti MS, Pini-Prato G, Cortellini P. Periodontal regeneration of human intrabony defects. IV. Determinants of healing response. J Periodontol 1993;64:934–940.
26. Cortellini P, Carnevale G, Sanz M, Tonetti MS. Treatment of deep and shallow infrabony defects. A multicenter randomized controlled clinical trial. J Clin Periodontol 1998;25: 981–987.
27. Tsitoura E, Tucker R, Suvan J, Laurell L, Cortellini P, Tonetti M. Baseline radiographic defect angle of the intrabony defect as a prognostic indicator in regenerative periodontal surgery with enamel matrix derivative. J Clin Periodontol 2004;31:643–647.
28. Kim C-K, Choi S-H, Kim T-S, Kaltschmitt J, Eickholz P. The infrabony defect and its determinants. J Periodont Res 2006;41:498–502.
29. Cortellini P, Tonetti MS. Evaluation of the effect of tooth vitality on regenerative outcomes in infrabony defects. J Clin Periodontol 2001;28:672–679.
30. Tonetti MS, Cortellini P, Suvan JE, Adrians P, Baldi C, Dubravec D et al. Generalizability of the added benefits of guided tissue regeneration in the treatment of deep infrabony defects. Evaluation in a multi-center randomized controlled clinical trial. J Periodontol 1998;69:1183–1192.
31. Tonetti MS, Cortellini P, Lang NP, Suvan JE, Adrians P, Dubravec D et al. Clinical outcomes following treatment of human intrabony defects with GTR/bone replacement material or access flap alone. A multicenter randomised controlled clinical trial. J Clin Periodontol 2004;31:770–776.
32. Hamp S-E, Nyman S, Lindhe J. Periodontal treatment of multirooted teeth. Results after 5 years. J Clin Periodontol 1975;21:126–135.
33. Proestakis G, Bratthall G, Söderholm G, Kullendorff B, Gröndahl K, Rohlin M, Attström R. Guided tissue regeneration in the treatment of infrabony defects on maxillary premolars. A pilot study. J Clin Periodontol 1992;19:766–773.
34. McGuire MK, Nunn ME. Prognosis versus actual outcome. III. The effectiveness of clinical parameters in developing an accurate prognosis. J Periodontol 1996;67:666–674.
35. Eickholz P. Glossar der Grundbegriffe für die Praxis. Regenerative Parodontaltherapie. Teil 2: Indikationen. Parodontologie 2005;16(4):337–340.
36. Horwitz J, Machtei EE, Reitmeir P, Holle R, Kim T-S, Eickholz P. Radiographic parameters as prognostic indicators for healing of class II furcation defects. J Clin Periodontol 2004;31: 105–111.
37. Eickholz P. Glossar der Grundbegriffe für die Praxis. Regenerative Parodontaltherapie. Teil 3: Membrantypen: nichtresorbierbar und biologisch abbaubar. Parodontologie 2006;17(2):181–189.
38. Esposito M, Grusovin MG, Coulthard P, Worthington HV. Enamel matrix derivative (Emdogain®) for periodontal regeneration in intrabony defects. Cochrane Database Syst Rev. 2005;19(4):CD003875.
39. Christgau M, Schmalz G, Reich E, Wenzel A. Clinical and radiographical split-mouth-study on resorbable versus non-resorbable GTR-membranes. J Clin Periodontol 1995;22:306–315.
40. Yukna CN, Yukna RA. Multi-center evaluation of bioabsorbable collagen membrane for guided tissue regeneration in human class II furcations. J Periodontol 1996;67:650–657.
41. Caffesse RG, Mota L, Quinones C, Morrison E. Clinical comparison of resorbable and non-resorbable barriers for guided tissue regeneration. J Clin Periodontol 1997;24:747–752.
42. Garrett S, Polson AM, Stoller NH, Drisko CL, Caton JG, Harrold CQ et al. Comparison of a bioabsorbable GTR barrier to a non-absorbable barrier in treating human class II furcation defects. A multi-center parallel design randomized single-blind trial. J Periodontol 1997;68:667–675.
43. Eickholz P, Kim T-S, Holle R. Regenerative periodontal surgery with non-resorbable and biodegradable barriers: Results after 24 months. J Clin Periodontol 1998;25:666–676.
44. Jepsen S, Heinz B, Jepsen K, Arjomand M, Hoffmann T, Richter S et al. A randomized clinical trial comparing enamel matrix derivative and membrane treatment of buccal class II furcation involvement in mandibular molars. Part I: Study design and results for primary outcomes. J Periodontol 2004; 75:1150–1160.
45. Hoffmann T, Richter S, Meyle J, Gonzales JR, Heinz B, Arjomand M et al. A randomized clinical multicenter trial comparing enamel matrix derivative and membrane treatment of buccal class II furcation involvement in mandibular molars. Part III: Patient factors and treatment outcome. J Clin Periodontol 2006;33:575–583.
46. Cortellini P, Pini Prato G, Tonetti MS. The modified papilla preservation technique. A new surgical approach for interproximal regenerative procedures. J Periodontol 1995;66:261–266.
47. Eickholz P, Kim T-S, Steinbrenner H, Dörfer C, Holle R. Guided tissue regeneration with bioabsorbable barriers: Intrabony defects and class II furcations. J Periodontol 2000; 71:999–1008.

48. Mombelli A, Zappa U, Brägger U, Lang NP. Systemic antimicrobial treatment and guided tissue regeneration. Clinical and microbiological effects in furcation defects. J Clin Periodontol 1996;23:386–396.
49. Eickholz P, Lenhard M, Benn DK, Staehle HJ. Periodontal surgery of vertical bony defects with or without synthetical bioabsorbable barriers. 12 months' results. J Periodontol 1998;69:1210–1217.
50. Vest TM, Greenwell H, Drisko C, Wittwer JW, Bichara J, Yancey J et al. The effect of postsurgical antibiotics and a bioabsorbable membrane on regenerative healing in class II furcation defects. J Periodontol 1999; 70:878–887.
51. Heden G, Wennström J, Lindhe J. Periodontal tissue alterations following Emdogain treatment of periodontal sites with angular bone defects. A series of case reports. J Clin Periodontol 1999;26:855–860.
52. Sculean A, Blaes A, Arweiler N, Reich E, Donos N, Brecx M. The effect of postsurgical antibiotics on the healing of intrabony defects following treatment with enamel matrix proteins. J Periodontol 2001;72:190–195.
53. Sculean A, Berakdar M, Donos N, Auschill TM, Arweiler NB. The effect of postsurgical administration of a selective cyclooxygenase-2 inhibitor on the healing of intrabony defects following treatment with enamel matrix proteins. Clin Oral Investig 2003;7:108–112.
54. Murphy K. Interproximal tissue maintenance in GTR procedures. A new surgical technique and 1-year reentry results. Int J Periodontics Restorative Dent 1996;16:463–477.
55. Takei HH, Han TJ, Carranza FA jr, Kenney EB, Lekovic V. Flap technique for periodontal bone implants. Papilla preservation technique. J Periodontol 1985;56:204–210.
56. Cortellini P, Pini Prato G, Tonetti MS. The simplified papilla preservation flap. A novel surgical approach for the management of soft tissues in regenerative procedures. Int J Periodontics Restorative Dent 1999;19:589–599.
57. Eickholz P. Glossar der Grundbegriffe für die Praxis. Chirurgische Parodontitistherapie. 3. Papillenerhaltungslappen – klassisch, modifiziert und vereinfacht. Parodontologie 2003;14(4):411–418.
58. Machtei EE. The effect of membrane exposure on the outcome of regenerative procedures in humans: A meta-analysis. J Periodontol 2001;72:512–516.
59. Axelsson P, Lindhe J. The significance of maintenance care in the treatment of periodontal disease. J Clin Periodontol 1981;8:281–294.
60. Pretzl B, Eickholz P. Langzeitergebnisse 10 Jahre nach parodontaler Therapie. 1. Patientenbezogene Faktoren. Dtsch Zahnärztl Z 2005;60:207–210.

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