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Guided Tissue Regeneration: A Decision-Making Model

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Abstract

Background: Guided tissue regeneration (GTR) has the potential to promote periodontal regeneration, which is one of the goals of periodontal surgery. While many successful reports of periodontal regeneration using barrier membranes exist in the literature, considerable heterogeneity of GTR outcomes is more typical of current reports. The reasons for this variability are numerous, but could be attributed to differences in surgical skills and case selection. There is a need for a current analysis of the factors affecting success and the formation of evidence-based treatment guidelines for GTR. **Methods:** Available English literature pertaining to guided tissue regeneration was reviewed. Sources included peer-reviewed journal publications, online resources, and textbooks. Specific consideration was made to factors affecting GTR outcomes, especially in the context of systematic reviews and meta-analyses. **Results:** Factors, including patient systemic conditions and compliance, defect features, local factors and surgical techniques and materials, that influence GTR outcomes were analyzed and entered into a decision-making model. **Conclusion:** A decision-making model was formulated based upon current evidence regarding factors that influence guided tissue regeneration outcomes. Meticulous case selection based upon known influential variables may help to minimize inconsistency in GTR outcomes.

Introduction

Guided tissue regeneration (GTR) using barrier membranes with or without bone substitute graft materials is based on the concept of epithelial exclusion in order to promote the healing of periodontal tissues in such a way that the original structure and function is preserved (Melcher, 1976). This is preferable to tissue repair, which merely replaces lost tissue with less specialized tissue and does not completely restore tissue function. In periodontal situations, formation of a long junctional epithelium is the most common form of tissue repair and a typical outcome of traditional periodontal surgery (Caton and Zander, 1979). While tissue regeneration is an ideal outcome of periodontal surgery, attempts at GTR show a wide range of predictability in the literature.

Many studies comparing GTR to traditional open flap debridement (OFD) surgery showed that GTR generally resulted in much greater clinical attachment level (CAL) gain than OFD. In a series of classic studies, Cortellini and colleagues compared GTR using expanded polytetrafluoroethylene (ePTFE) membranes to OFD surgery and reported a remarkable 5.2 mm gain in CAL in the GTR group compared to 2.3 mm in the control group (Cortellini *et al.*, 1996b). A related study evaluating ePTFE titanium-reinforced membranes showed a similar advantage with the GTR group experiencing a 5.3 mm CAL gain compared with 2.5 mm in the control OFD group (Cortellini and Bowers, 1995). Similarly, the use of bioabsorbable membranes resulted in superior CAL gains, with one study reporting 3.1 mm CAL gain using a polylactic/polyglycolic (PLA/PGA) membrane compared to 1.7 mm of CAL gain in the control OFD group (Sculean *et al.*, 2001). However, in contrast to these promising studies, several reports failed to find any significant benefit of using GTR. One group found that GTR using an ePTFE membrane resulted in 2.4 mm gain of CAL compared with 2.2 mm using OFD (Nygaard-Ostby *et al.*, 1996). Another study comparing GTR using a polylactic acid (PLA) membrane to OFD reported better outcomes in the OFD group, where a 3.33 mm CAL gain was noted compared to 3.13 mm gain in the GTR group (Ratka-Kruger *et al.*, 2000). Furthermore, Blumenthal and Steinberg reported only modest CAL gains of 1.17 mm using a bioabsorbable bovine collagen membrane, which was not significantly different from the 0.75 mm CAL gain in the control OFD group (Blumenthal and Steinberg, 1990). As more

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information is learned regarding factors that influence GTR outcomes, more predictable results are expected to be obtained. However, a recent comparison between the variability in clinical outcomes between OFD and GTR revealed that, while GTR was slightly more predictable than OFD, there was still a wide range of outcomes (Aichelmann-Reidy and Reynolds, 2008).

There are many possible reasons for the heterogeneity of GTR success rates reported in the literature. That GTR is a highly technique-sensitive surgical skill certainly influences the outcome (Tonetti *et al.*, 1998). Another important factor influencing GTR outcomes is patient selection. Many aspects of a patient, including systemic conditions, etiology of the defect, local factors, defect morphology, surgical technique, and post-surgical factors can contribute to GTR success or failure. Consequently, an awareness of the factors that affect GTR outcomes is critical in deciding whether or not to pursue this therapy. This paper provides current information on the factors influencing GTR success and presents a decision-making model to help increase the predictability of GTR as a treatment modality.

Presence of acquired diseases

GTR is a highly delicate procedure that relies on the body's ability to heal in an optimum way. Consequently, patients with compromised healing potential are not good candidates for GTR procedures. Systemic conditions that may preclude a patient from undergoing periodontal surgery include, but are not limited to, uncontrolled diabetes mellitus, cancer, recent radiation to the head and neck region, acquired immunodeficiency syndrome (AIDS), or other conditions causing immunosuppression (Campo *et al.*, 2007; Escoda-Francoli *et al.*, 2010; Jegoux *et al.*, 2010; Retzepi *et al.*, 2010). *Figure 1* shows a decision tree for determining if a patient meets the systemic requirements to undergo GTR procedures.

Environmental/behavioral factors

Another systemic factor to consider is a patient's smoking status. In a retrospective study of 71 periodontal defects treated with GTR, smoking more than 10 cigarettes per day was associated with significantly less CAL gain at 1 year (2.1 mm vs. 5.2 mm) (Tonetti *et al.*, 1995). Another study comparing smokers to non-smokers reported a CAL gain of 1.9 mm in non-smokers compared to 0.8 mm in smokers (Mayfield *et al.*, 1998). Similarly, a study by Rosenberg and Cutler found that 80% of GTR failures were in smokers (Rosenberg and Cutler, 1994). Some authors suggest that better results can be obtained in smokers if an aggressive antimicrobial regimen is pursued (Machtei *et al.*, 2003); however, the results obtained using this regimen are still not as favorable as what can be obtained in non-smokers. In summary, patients who smoke are not good candidates for GTR surgery, even if antimicrobial therapy or a smoking cessation protocol is initiated around the time of surgery since the effects of smoking are detrimental up to 12 months post-surgically, as was demonstrated in the studies discussed above.

Patient compliance and stress are also considerations that may contribute to the outcomes of GTR. Long-term follow-up of patients who received GTR therapy found that patients who were non-compliant with recall appointments had a 50 times greater risk for attachment loss between 1 and 4 years after surgery (Cortellini *et al.*, 1994). Similarly, stress and inadequate coping behaviors were associated with an increased risk for developing severe periodontal disease (Genco *et al.*, 1999). Thus, careful consideration of the patient's overall physical and emotional status is important as part of appropriate case selection.

Developmental conditions/diseases

Among various systemic factors, genetic conditions altering wound healing and collagen synthesis should also be evaluated. Ehlers-Danlos syndrome is a condition characterized by defective fibroblast migration resulting in impaired wound healing (Viglio *et al.*, 2008). Specific interleukin-1 (IL-1) genotype polymorphisms have been shown to negatively affect the long-term stability of GTR therapy. One study evaluated the influence of the IL-1 polymorphism in patients receiving GTR therapy (De Sanctis and Zucchelli, 2000). After 3 years, patients with the polymorphism experienced a 50% relapse in clinical attachment loss, despite initial improvement after surgery. In addition, they were ten times more likely to experience a 2 mm loss of attachment compared to genotype-negative controls.

Etiology of periodontal osseous defects

In general, periodontal defects are the result of bacterial plaque in a susceptible host. If a periodontal defect is to be effectively treated using GTR, the etiologic factors must first be removed and controlled (*Figure 2*). Classic studies have demonstrated that optimal healing can occur after conventional periodontal surgery if excellent plaque control is present during surgery and throughout the healing phase (Rosling *et al.*, 1976a; Rosling *et al.*, 1976b). In contrast, significant attachment loss and recurrence of periodontal pockets occurred after periodontal surgery if patients could not perform proper plaque control (Nyman *et al.*, 1977). Since GTR is even more sensitive to bacterial contamination, and because of the detrimental effects on healing, only patients with excellent oral hygiene should be candidates for this procedure. One study evaluated GTR outcomes for a period of 5 years post-surgically (Cortellini *et al.*, 1996a). Their results showed that patients with a full mouth plaque score (FMPS) > 10% had poorer outcomes and experienced attachment loss over time.

It is also important to consider the periodontal condition of the entire dentition. Periodontal infection

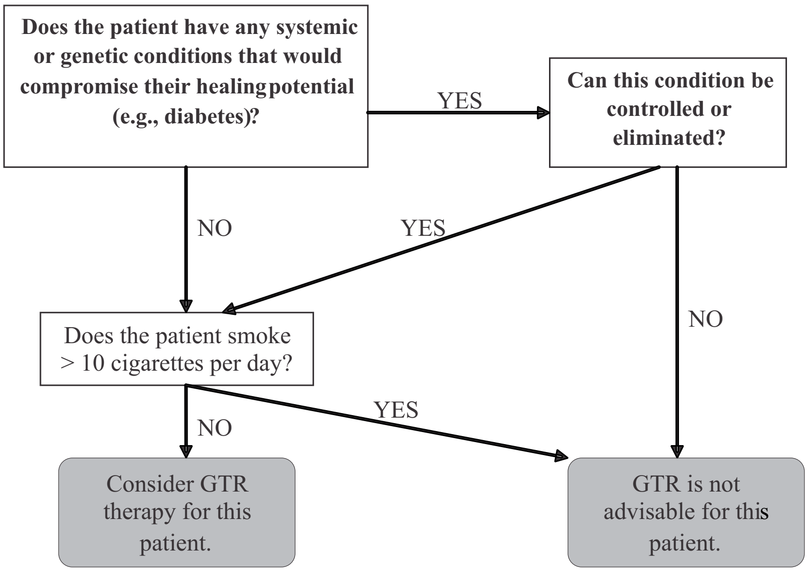

Figure 1. Decision tree to determine if a patient is a candidate for GTR based upon their systemic conditions.

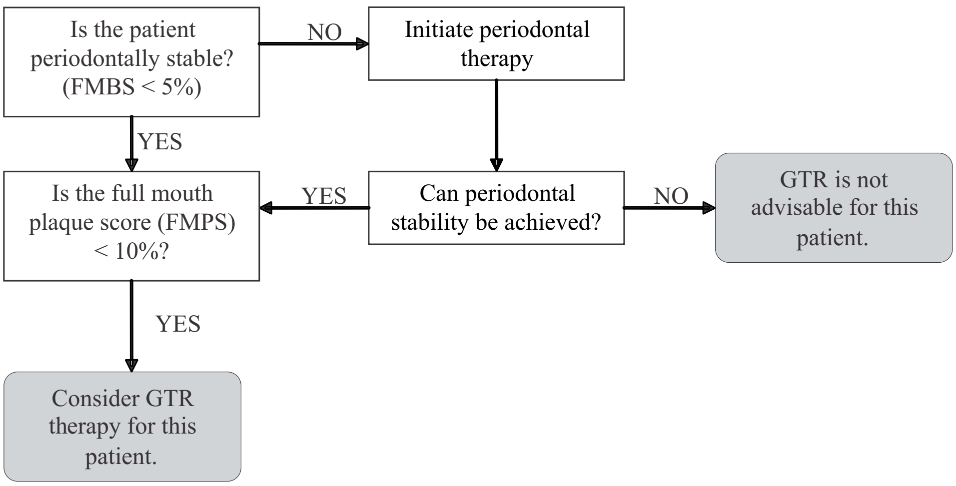

Figure 2. Decision tree to determine if a patient is a candidate for GTR based upon etiologic factors and their ability to be controlled.

present anywhere in the mouth can have an adverse effect on GTR therapy. Tonetti and colleagues found that the full mouth bleeding score (FMBS), which has a high negative predictive value for periodontal health (Lang *et al.*, 1990), was an important predictor of GTR outcome (Tonetti *et al.*, 1993). Hence, it is important to ensure periodontal stability of the remaining dentition prior to initiating GTR therapy. Ideally, initial therapy should be completed first, followed by any conventional periodontal surgery to achieve maximal periodontal stability prior to initiating GTR therapy.

Local factors

In addition to controlling systemic and etiological factors, it is important to establish a local environment that is conducive to periodontal regeneration (*Figure 3*). Local factors that prevent connective tissue attachment, such as crowns, restorations with apical margins, enamel pearls, cervical enamel projections (CEPs), and bifurcation ridges should be identified and removed if possible as part of the GTR procedure (Mardam-Bey *et al.*, 1991). Provided that these factors can be removed, their initial presence has been shown to have no detrimental effect on GTR outcomes (Tsao *et al.*, 2006). If it is impossible to remove a particular local factor, such as an amalgam restoration with a deep margin, then GTR is contra-indicated for that area.

The amount and thickness of keratinized gingiva present in the area of the defect should also be assessed. One study showed that thick (> 1.1 mm) keratinized

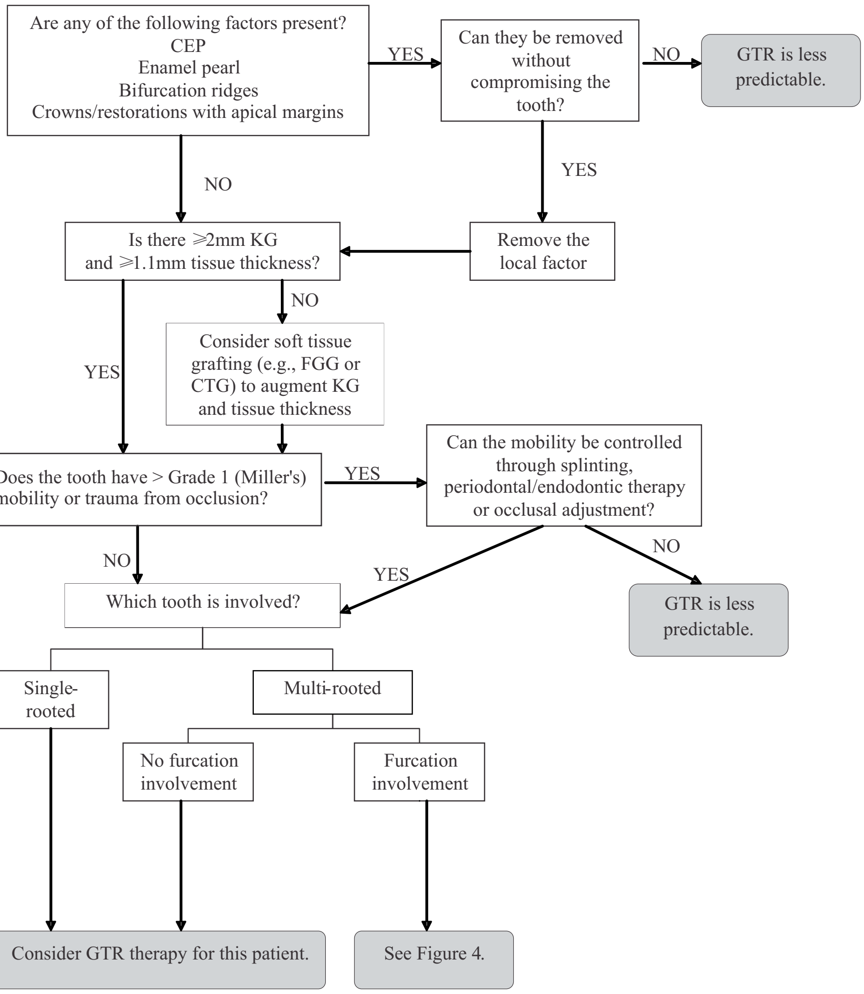

Figure 3. Decision tree to determine if a patient is a candidate for GTR (guided tissue regeneration) based upon local factors. CTG, connective tissue graft; FGG, free gingival graft; KG, keratinized gingiva

gingiva is associated with success in coronally positioned flap procedures (Hwang and Wang, 2006). Coronally positioning a flap over a barrier membrane or furcation entrance is often a feature of GTR procedures. Wang and Boyapati proposed four principles necessary for successful GBR: primary wound closure, angiogenesis, space creation, and wound stability (Wang and Boyapati, 2006). The presence of thick keratinized gingiva could certainly aid in primary wound closure and angiogenesis, and, therefore, this may be an important factor to consider. In one study, flap dehiscence over a barrier membrane was associated with thin gingival tissue (< 1 mm) (Anderegg *et al.*, 1991). In cases where thin or insufficient keratinized gingiva is present, mucogingival surgery is strongly recommended prior to GTR to augment the soft tissue.

The mobility of the tooth also needs to be evaluated. A classic study by Flezsar showed an inverse relationship between tooth mobility and CAL gain after periodontal surgery (Fleszar *et al.*, 1980). A more recent study involving GTR confirmed this trend (Cortellini *et al.*, 2001). Wang and Boyapati suggested that wound stability was a key feature of successful GTR outcomes (Wang and Boyapati, 2006) and so, ideally, there should be no mobility of the tooth in question. However, one study suggested that slight mobility may not compromise the success of GTR procedures (Trejo and Weltman, 2004). Importantly, the cause of tooth mobility needs to be determined. Causes may include occlusal trauma, infection, or periodontal bone loss. If possible, the mobility should be reduced through minimally invasive techniques such as occlusal adjustment, splinting, or periodontal or endodontic therapy. If the tooth remains hypermobile, defined as Miller's class 2 or 3 mobility, then a successful outcome cannot be expected and GTR should not be pursued.

Finally, specific morphological characteristics of the tooth may affect the outcome of GTR therapy. A systematic review showed that GTR treatment produced significantly better outcomes than OFD in mandibular furcations; however, when comparing GTR to OFD in maxillary furcations, the GTR group exhibited only slightly better, although statistically significant, outcomes (Jepsen *et al.*, 2002). Thus, mandibular furcations may be slightly more amenable to positive GTR outcomes than maxillary furcations. Another study supported this claim with the greatest

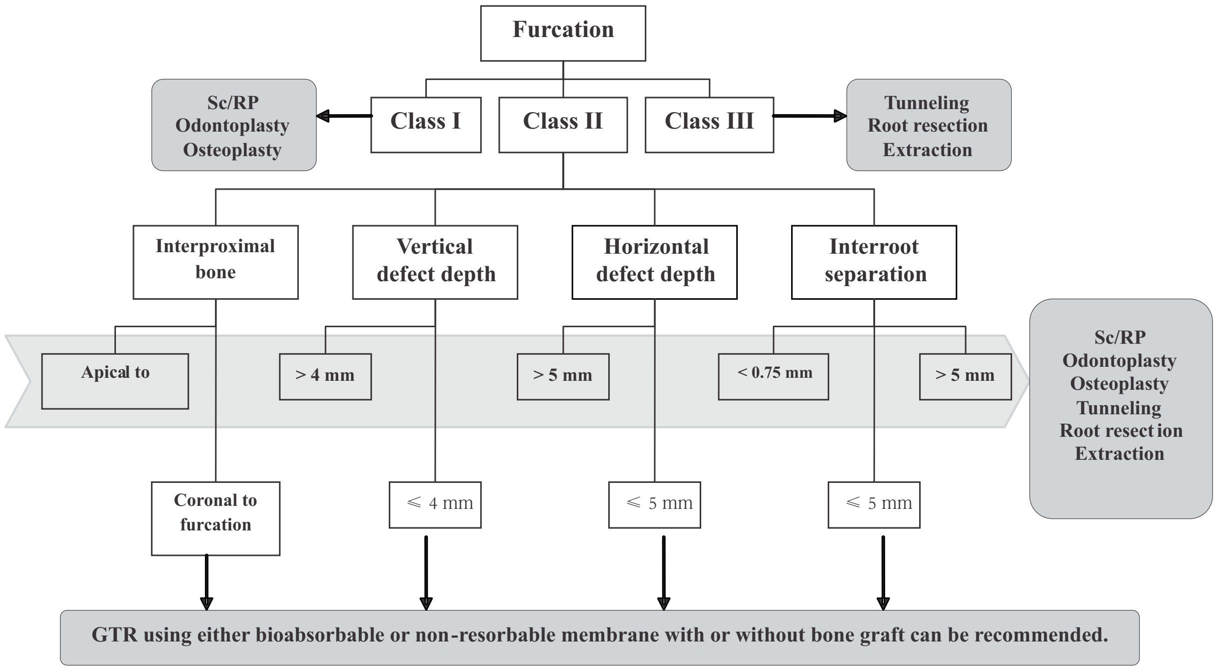

Figure 4. Decision tree for the treatment of furcation defects including suggested treatment options based upon defect characteristics.

clinical improvements reported for mandibular molars, followed by the buccal furcation of maxillary molars (Pontoriero and Lindhe, 1995a; b). Also, infrabony defects on the distal of maxillary molars may be more difficult to treat because access is difficult and the furcation area can act as a reservoir of bacteria. This was confirmed by Pontoriero and Lindhe, who noted little to no clinical improvement on maxillary interproximal furcations after GTR treatment (Pontoriero and Lindhe, 1995a; b). However, no difference was observed, regarding GTR outcome, between first and second molars (Machtei *et al.*, 1994). Finally, surgical access on anterior teeth may be easier than on posterior teeth, although there is no direct evidence that this affects GTR outcomes.

Defect morphology

GTR is indicated for the treatment of two main periodontal defects: furcations and infrabony defects. The specific characteristics of each of these defects may determine if a GTR procedure will be successful for that particular tooth. *Figure 4* presents a decision tree with treatment suggestions for different characteristics of furcation defects. *Figure 5* presents treatment suggestions for intrabony defects. As a general rule, factors that position the regenerative cells in close proximity to the area to be regenerated increase the chance of success of GTR.

Furcation defects

GTR treatment is ideally suited to the treatment of Class II furcations. Class I furcations are typically too small for GTR to be effective, whereas Class III furcations are too advanced for GTR procedures to result in any predictably appreciable gain. Thus, for Class I and III situations, other treatment avenues should be considered, such as osteoplasty or tunneling. Specific characteristics of a Class II furcation are also predictive of GTR success, including interproximal bone height, horizontal and vertical defect depth, and root separation.

Interproximal bone can provide a source for regenerative cells, as well as allow for effective coronal positioning of the flap over the membrane (Horwitz *et al.*, 2004). One study showed that if the interproximal bone was coronal to the furcation, then complete closure could be achieved in 94% of cases compared with 70% if it was apical to the furcation (Horwitz *et al.*, 2004). A similar finding demonstrated that supra-osseous defects were associated with poorer outcomes than intra-osseous defects (Machtei and Schallhorn, 1995). Accordingly, cases selected for GTR therapy should have interproximal bone coronal to the furcation entrance.

In general, the larger the defect, the more difficult it is to regenerate. Defect dimensions that should be assessed include the vertical and horizontal defect depth as well as the degree of root separation. Horizontal or vertical furcation defects equal or greater than 5 mm responded with the lowest frequency of complete clinical closure (Bowers *et al.*, 2003). Thus, if the inter-root distance is wide enough that bone loss in the area would result in a critical-size defect that cannot spontaneously heal, the regenerative potential is lower because the cells critical for regeneration are too remote to repopulate the wound (Horwitz *et al.*, 2004).

Infrabony defects

The main factors influencing GTR outcomes in

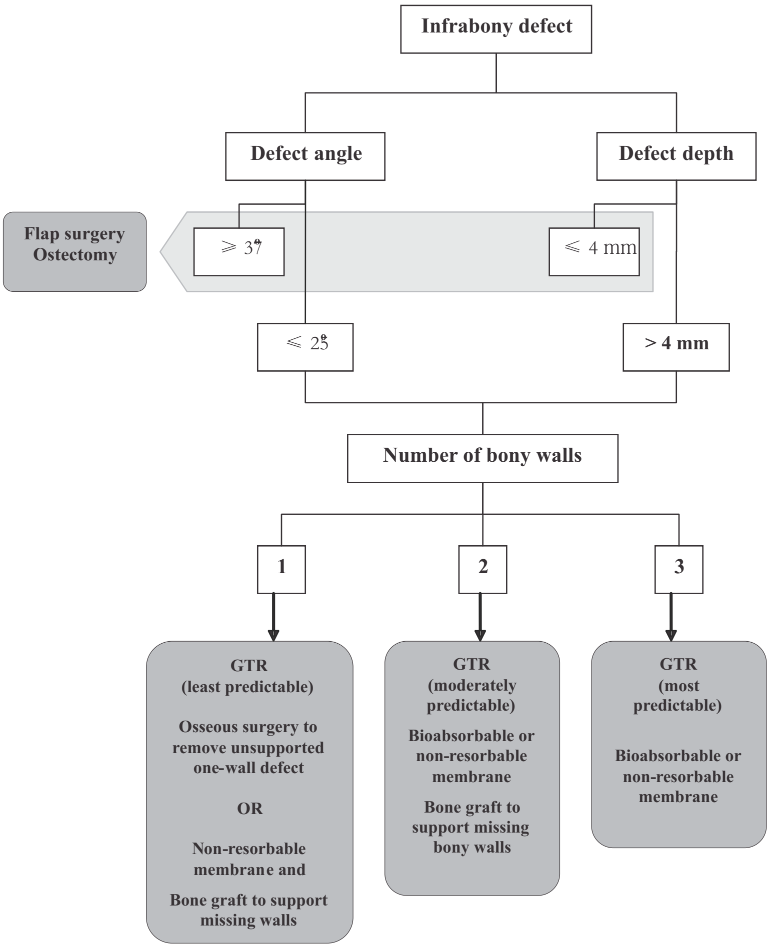

Figure 5. Decision tree for the treatment of infrabony defects including suggested treatment options based upon defect characteristics.

infrabony defects are the depth, number of residual walls, and angle associated with the defect. A deep, narrow, self-contained defect serves both to protect the area by stabilizing the wound and also to keep regenerative cells in close approximation. A wider, shallow defect has an increased risk of coagulum displacement and wound instability, and, therefore, these defects are not as amenable to GTR procedures (Cortellini and Tonetti, 2000). However, one recent animal study suggested that both deep/wide and narrow/shallow infrabony defects had high potential for regeneration (Stavropoulos and Wikesjo, 2010). Studies evaluating defect angles show that if the angle between the tooth and the defect is ⩽ 25 degrees, GTR is indicated (Cortellini and Bowers, 1995). In contrast, wide defect angles (⩾ 37 degrees) are not associated with predictable GTR outcomes (Tonetti *et al.*, 1993). On average, 1.5 mm more attachment can be expected in narrow defects. Correspondingly, shallow (⩽ 4 mm) defects are less predictable than deep (> 4 mm) defects (Laurell *et al.*, 1998). The number of bony walls present in the defect can also influence success. The greater the number of walls (3>2>1), the easier it is to maintain space and wound stability. Most studies support the idea that 3-wall defects have the best clinical results (Becker and Becker, 1993; Handelsman *et al.*, 1991; Selvig *et al.*, 1993), although two studies failed to find a correlation between GTR success and the number of bony walls (Tonetti *et al.*, 1993; Tonetti *et al.*, 1996). In cases where the defect is not well contained, GTR may be successful but a titanium-reinforced membrane to help maintain space may be preferable in these situations. Studies evaluating GTR in defects with unfavorable architecture, such as one-wall defects, have shown that successful outcomes are possible but not predictable (Aimetti *et al.*, 2005).

Surgical technique

Primary and passive closure of the flap is critical for GTR success in order to promote wound stability and to prevent premature membrane exposure and secondary intention healing (Wang and MacNeil, 1998; Wang and Boyapati, 2006). Incisions designed to keep the interdental papilla intact may be useful for GTR applications including the modified papilla preservation technique (Cortellini *et al.*, 1995) and the simplified papilla preservation flap (Cortellini *et al.*, 1999). While a recent systematic review found no statistical difference between GTR cases treated using a papilla preservation technique and other flap designs, there was an overall greater improvement of 0.75 mm CAL gain using the papilla preservation technique with a trend towards significance ($p = 0.09$, Needleman *et al.*, 2006). Cortellini and colleagues suggested using the modified papilla preservation technique when interdental spaces were wide (>2 mm) and the simplified papilla preservation flap for narrow (<2 mm) interdental spaces (Cortellini and Tonetti, 2000).

The decision to use a membrane, bone substitute graft, or a combination is an important consideration. A systematic review of the treatment of infrabony defects found that no difference in clinical outcome was observed between particulate bone allografts and hydroxyapatite ceramic grafts (Reynolds *et al.*, 2003). Furthermore, additional CAL gain was found when the bone substitute graft was combined with a barrier membrane (Reynolds *et al.*, 2003). While a membrane may augment a bone substitute graft, the reverse is not true. Results reported in another systematic review asserted that a bone substitute graft plus a membrane was necessary for optimal results in furcation areas, although they found no additional benefit to using a bone substitute graft in infrabony defects where a membrane was used (Murphy and Gunsolley, 2003). Another systematic review found no difference in outcomes whether a non-resorbable or bioabsorbable membrane was used (Needleman *et al.*, 2006), although a trend towards slightly better CAL gains were noted for the non-resorbable group (p=0.11). Non-resorbable membranes and the use of a bone substitute graft can help to maintain or create space, and should be employed in areas such as shallow, 1-wall defects where predictability is less certain. In areas where the anatomy is more favorable for regeneration, any membrane may be used successfully. Using computed tomography (CT) imaging to aid in ideal membrane placement was suggested by one group in order to improve surgical efficiency and accuracy (Takane *et al.*, 2010).

Autogenous periosteal grafts may be used as an alternative to synthetic barrier membranes. A recent report using autogenous periosteal membranes showed less gingival recession than collagen membranes (Paolantonio *et al.*, 2010). One study reported similar outcomes between connective tissue grafts that included the periosteum and open flap debridement (Kwan *et al.*, 1998). Recently, a clinical trial found that the use of a marginal periosteal pedicle graft resulted in infrabony defect reduction with an average bone gain of 2.2 mm (Gamal and Mailhot, 2008).

Growth factors such as emdogain (EMD), platelet-rich plasma (PRP), platelet-derived growth factor (PDGF), bone morphogenic proteins (BMPs) and fibroblast growth factor (FGF-2) have been studied for their ability to additionally improve the effects of GTR. A meta-analysis comparing EMD to EMD and GTR combined actually found that EMD alone produced better clinical results (Venezia *et al.*, 2004). Studies comparing a combination of EMD and GTR with either treatment alone found that the combined therapy imparted no clinical advantage (Minabe *et al.*, 2002; Sculean *et al.*, 2001; Sculean *et al.*, 2004; Sipos *et al.*, 2005). PDGF has also shown promise in promoting periodontal regeneration (Nevins *et al.*, 2005). In addition, BMP-2 was shown to promote bone regeneration around implants (Jung *et al.*, 2003; Jung *et al.*, 2009). Insufficient data exists to draw conclusions about PRP and FGF-2, and so no recommendation is made for these adjunctive materials. An advantage to using growth factors is that they are simple to apply and are not as technique-sensitive as GTR procedures. Thus, they may be a preferred approach in situations where GTR and growth factors would produce similar results. However, due to the high cost of these materials, it is important to evaluate the cost-benefit ratio when considering this treatment option.

Post-surgical factors

The most critical factor for the long-term success of GTR procedures is optimal oral hygiene and an effective supportive periodontal maintenance program. Numerous studies support the idea that multiple factors contribute to initial GTR success, but that maintaining a good outcome over time is dependent on exceptional plaque control (Cortellini *et al.*, 1994; Machtei *et al.*, 1994). While frequent maintenance intervals, as often as bi-monthly, are commonly used in research studies, this may not always be practical in a clinical setting. A recent systematic review found that a 3 month maintenance interval did not significantly affect GTR outcomes, suggesting that this may be an acceptable maintenance regimen (Needleman *et al.*, 2005).

Other factors that may negatively influence GTR outcomes are membrane exposure and post-operative infection. Membrane exposure is a common occurrence, especially when non-resorbable membranes are used, with studies reporting incidence rates of 33-68% (Mayfield *et al.*, 1998; Sculean *et al.*, 2001; Zucchelli *et al.*, 2002). While a more recent study suggests that membrane exposure itself does not influence GTR outcomes (Cortellini *et al.*, 2001), it may necessitate a more stringent plaque control regimen and the need for prophylactic antibiotics. This idea is supported by a study that found an inverse correlation between bacterial contamination of ePTFE membranes at the time of removal and CAL gain 12 months post-surgically (Selvig *et al.*, 1992). While membrane exposure is not a desirable outcome of GTR surgery, it is unlikely to cause failure of the procedure as long as the area remains uncontaminated with plaque. Thus, antimicrobial rinses, systemic antibiotics, and more frequent recall intervals should be considered for these patients.

Conclusion

Not all patients or teeth are ideal candidates for GTR procedures. Careful case selection and attention to surgical detail are critical for successful outcomes using GTR. In general, systemically healthy non-smokers with optimal oral hygiene and excellent compliance can expect successful outcomes. Ideal teeth for this procedure should have no mobility, sufficient keratinized gingiva, higher interproximal bone height and narrow, deep, 3-wall defects. Surgical procedures that minimize membrane exposure, maintain space and stability, and minimize tissue trauma should be employed when possible. Since GTR is such a technique-sensitive procedure, it is imperative that cases are carefully chosen based on the above decision model in order to expect successful outcomes.

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