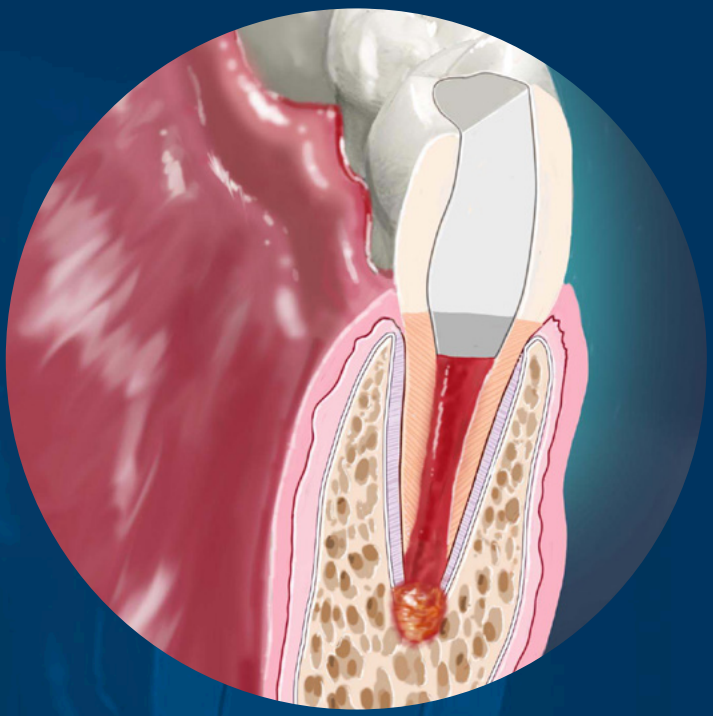
# Regenerative Endodontics



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# ENDODONTICS:

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## What is regenerative endodontics?

The management of immature permanent teeth with pulpal necrosis is challenging because the root canal system is often difficult to debride and the thin dentinal walls are at an increased risk of a subsequent cervical fracture (1). When a cervical root fracture occurs, this results in a restorative dilemma, since implants are generally contraindicated in young patients with a growing craniofacial skeleton. Therefore, alternative treatment approaches have evolved that that build on the principles of regenerative medicine and tissue engineering, which aim to successfully treat these challenging cases by attempting to regenerate functional pulpal tissue. These protocols are referred to as regenerative endodontic procedures (REPs).

Regenerative endodontic procedures have been defined as "biologically based procedures designed to replace damaged structures, including dentin and root structures, as well as cells of the pulp-dentin complex'' (2). In the immature tooth with pulpal necrosis, this optimally will result in complete restoration of pulpal function and subsequent completion of root development (3). Case studies have shown that healing of apical periodontitis, continued development of the root apex and increased thickness of the root canal wall of immature teeth with pulpal necrosis can occur after REPs. Figure 1 is an example of a tooth (#29) diagnosed with a dens evaginatus and with apical periodontitis that had a REP done with the one year follow up.

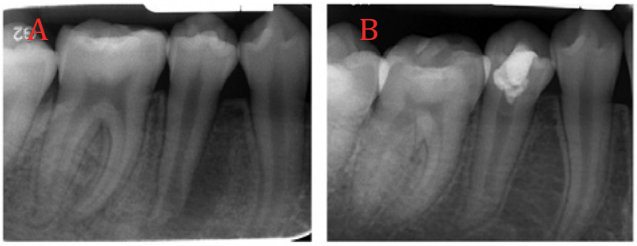


**Figure 1.** (A) Preoperative radiograph of tooth #29. (B) One year follow up after regenerative endodontic treatment (Courtesy: Dr. Avina Paranjpe, Seattle, WA)

Regenerative endodontic procedures evolved from early experiments on the role of the blood clot in endodontic therapy (4), coupled with an understanding that revascularization, or reestablishment of a vascular supply to existing pulp tissue, is essential for continuation of root development after traumatic injuries (5, 6). Other contributing factors in the evolution of REPs have come from the expansion of stem cell research, the discovery of mesenchymal stem cells with the potential to differentiate into odontogenic cells lines (7-9) and the prospect of a myriad of potential therapeutic applications made possible by tissue engineering (9, 10).

## What is tissue engineering?

Tissue engineering is an interdisciplinary field that integrates the principles of biology and engineering to develop biological substitutes that can replace or regenerate human cells, tissues, or organs in order to restore or reestablish normal function (10). There are three key elements for tissue engineering: **stem cells, scaffolds** and **growth factors or signals** (Figure 2).

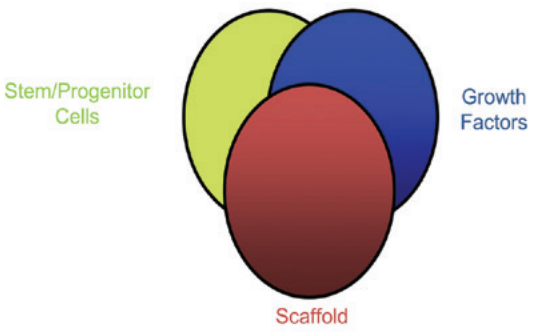


**Figure 2.** The three main components of tissue engineering (Hargreaves KM, Diogenes A, Teixeira FB. Treatment options: biological basis of regenerative endodontic procedures. J Endod. 2013 Mar;39(3 Suppl):S30-43. doi: 10.1016/j.joen.2012.11.025. PMID: 23439043; PMCID: PMC3589799.)

**Stem cells** are undifferentiated cells that continuously divide. There are two main types: embryonic stem cells and postnatal or adult stem cells. Embryonic stem cells are "multipotent" and can develop into more than 200 cell types. In contrast, adult stem cells are "pluripotent" and can only develop into a very limited number of cell types. Several subsets of adult stem cells have been isolated. These include dental pulp stem cells (DPSCs) (11), Postnatal human dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHEDs) (12), periodontal ligament stem cells (PDLSCs) (13), dental follicle progenitor stem cells (DFPCs) (14), and stem cells from apical papilla (SCAPs) (15, 16).

**Scaffolds** are three-dimensional microstructural environments that consists of biologically active compounds, which are necessary to facilitate tissue repair and regeneration by providing support for cell organization, proliferation, differentiation and vascularization (17). Current REPs utilize either a blood clot (18) or platelet-rich plasma (19) to provide a scaffold in the root canal. However, many other types of biodegradable or permanent scaffolds made of natural (collagen, hyaluronic acid, chitosan and chitin) or synthetic (polylactic acid, polyglycolic acid, tricalcium phosphate, hydroxyapatite) materials are available. (20, 21). Recently, hydrogel nanofibers, nanoparticles, bioceramic based scaffolds, natural extracellular

matrix (ECM) based scaffolds, composite scaffolds and various fibrin gels have been investigated for dental pulp tissue engineering and have shown promising results (22-24).

**Growth factors or signals** are proteins that bind to receptors on the cell and act as signals to induce cellular proliferation and/or differentiation (2). Examples of key growth factors in pulp and dentin formation include bone morphogenetic protein (25), transforming growth factor–beta (26) and fibroblastic growth factor (27). Current REPs aim to utilize growth factors found in platelets (19) and dentin (28). Studies have shown that dentin contains a number of bioactive molecules which, when released, play an important role in regenerative procedures (28, 29).

## What is the biological basis for regenerative endodontic therapy?

Historically, long term calcium hydroxide treatment was used for an immature tooth with pulpal necrosis to induce apexification and formation of a hard tissue apical barrier prior to placing an obturation material such as gutta-percha in the root canal system (30). While the success rate of calcium hydroxide apexification is reported to be as high as 95%, there are several associated problems (31). These include (1) the time required for formation of the calcified barrier (3-24 months)(30, 32, 33); (2) multiple appointments needed for reapplication of calcium hydroxide and; (3) the effect of long term calcium hydroxide on the mechanical properties of dentin (1, 34, 35). It has been proposed that long-term exposure to calcium hydroxide degrades the collagen and denatures the carboxylate and phosphate groups in dentin leading to a collapse in its structure (34). Moreover, the frequency of fracture was associated with the stage of root development with the highest frequency of fractures occurring in teeth with the least developed roots (1).

An alternate treatment involves using a bioceramic material, such as Mineral Trioxide Aggregate (MTA), to create an apical plug . When placed adjacent to the periradicular tissues bioceramic materials have been shown to induce the formation of cementum-like hard tissue and offers several advantages over calcium hydroxide apexification (36, 37). These include a reduction in treatment time and fewer patient visits which in turn facilitate the timely restoration of the tooth. Studies on MTA apexification report that the success rate of the treatment is as high as 94% (38). Prospective clinical trials comparing MTA apexification to calcium hydroxide apexification report that the success rate of the former is comparable to or higher than that of the latter (39, 40). Furthermore, the long term (≥2 years) success rates of MTA apexification have demonstrated positive outcomes (41, 42). One of the disadvantages of MTA is tooth discoloration which is why some prefer other bioceramic materials for this procedure (43).

However, neither treatment option fosters further root development (thickness and length), and immature teeth remain vulnerable to root fractures. Fracture was the primary cause of failure in teeth that underwent the MTA apexification procedure (41). Because regenerative endodontic procedures have the potential for increased root development, this may provide a potentially better resistance to fracture, which could then result in an increased long-term prognosis.

## What are the considerations for clinical regenerative endodontic procedures (REPs)?

Various regenerative endodontic treatment protocols have been associated with a successful clinical outcome. Common features of cases with successful clinical outcomes after REPs are (3, 44):

**Young patient**

**Pulp necrosis and immature apex**

**Minimal or no instrumentation of the dentinal walls**

**Placement of an intracanal medicament**

**Creation of a blood clot or protein scaffold in canal**

**Effective coronal seal**

Regenerative endodontic procedures often involves a two-step or multi-step approach (44). Figure 3 outlines the codes for regenerative endodontic procedures from the American Dental Association (ADA).

The first appointment is centered on proper endodontic access and disinfection of the root canal system. Upon confirming the absence of clinical signs and symptoms, the second appointment focuses on releasing growth factors from the dentin (e.g. by irrigating with EDTA), delivering stem cells into the root canal by stimulating

PULPAL REGENERATION

| | |
|---|---|
| D3355 | Pulpal regeneration - initial visit |
| D3356 | Pulpal regeneration - interim medication replacement |
| D3357 | Pulpal regeneration - completion of treatment |

**Figure 3.** ADA codes for pulpal regeneration procedures

bleeding (45), creating a scaffold (e.g. blood clot or platelet-rich plasma) (18, 19), and sealing the tooth by placing a pulp space barrier (e.g. Mineral Trioxide Aggregate or another Bioceramic material). This is followed by apermanent coronal restoration to prevent bacterial reinfection (46). At the second appointment, it is recommended to use a local anesthetic without a vasoconstrictor to better facilitate the stimulation of apical bleeding.

The American Association of Endodontists has developed treatment considerations based on a review of case studies that is available electronically:

***ConsiderationsForRegEndo_AsOfNov2022-4.pdf***

These considerations should be seen as one possible source of information and, given the rapid evolving nature of this field, clinicians should also actively review new findings elsewhere as they become available. In addition, it is important to recognize that treatment considerations have evolved based on preclinical investigations and clinical case studies and therefore provide a lower level of evidence than would be provided by controlled clinical trials. More recently a few randomized controlled trials have been published which have compared various methodologies used during REPs or to NSRCTs in mature teeth (47). However, more prospective randomized clinical trials are needed to provide unbiased evaluations of different REPs and potential adverse events, as well as consensus on appropriate methods to evaluate clinical outcomes of regenerative endodontic therapies in humans where histological evaluation is not feasible.


**Figure 4.** Four components needed for a successful regenerative outcome.

As more evidence becomes available, modification of REPs are evolving. For example, disinfection of the canal space has been shown to be a major factor that affects the prognosis of REPs (48-50). Hence, adequate disinfection is one of the primary objectives during REPs and has been added as an important part of the tissue engineering principles (Figure 4). Various materials have been used for this purpose. The triple antibiotic paste (TAP) originally used by Banchs and Trope (18) was found to be cytotoxic to stem cells at higher concentrations, however, the lower concentrations did not disinfect the canal space adequately (49, 51). That said, the use of antibiotic pastes have been shown to improve the success of REPs when compared to calcium hydroxide (52). Research is ongoing to develop alternatives to the current disinfecting agents (53). Previous research has demonstrated that chlorhexidine (CHX) can reduce the attachment of stem cells to dentin and be toxic to stem cells (54, 55), therefore the use of CHX should be avoided during REPs. The use of EDTA has been studied during REPs and research has demonstrated that EDTA conditioning of dentin promoted the adhesion, migration and differentiation of stem cells towards or onto dentin. Hence a final irrigation with EDTA during REPs has the potential to act favorably on new tissue formation within the root canal and increase the chance of success (56)and is included in the Considerations for Regenerative Endodontic Procedure protocol (stated in the previous section).

**Follow-up (6-, 12-, 24-months)**

- Clinical and Radiographic exam
  - No pain, soft tissue swelling or sinus tract (often observed between first and second appointments).
  - Resolution of apical radiolucency (often observed 6-12 months after treatment)
  - Increased width of root walls (this is generally observed before apparent increase in root length and often occurs 12-24 months after treatment).
  - Increased root length.
  - Positive Pulp vitality test response
  - Recommended yearly follow-up after the first 2 years
  - CBCT is highly recommended for initial evaluation and follow-up visits

**Figure 5.** Guidelines for clinical and radiographic follow-up evaluation after regenerative endodontic procedures.

Before commencing regenerative endodontic treatment, it is imperative that patients and legal guardians are informed that two or more appointments may be needed for regenerative endodontic therapy and that follow-up appointments are essential to evaluate the clinical outcome and radiographic outcomes (Figure 5). Pain, soft tissue swelling, or increasing radiolucency indicates failure of the procedure and an alternative treatment (apical barrier with a bioceramic material such as MTA or extraction) would be recommended.

## What are the outcomes of regenerative endodontic procedures?

The REP treatment approach has been widely accepted as a conservative option for young permanent teeth with immature roots and a pulp necrosis (18, 57). Successful clinical outcomes following REPs for immature permanent mandibular

premolar teeth with pulpal necrosis and periapical infection were reported in landmark case reports by Iwahu et al. (58) and Banchs and Trope (18) (Figure 6). Three important treatment factors were identified: disinfection of the root canal system, placement of a matrix in the canal for tissue in-growth and a bacterial tight seal of the access opening (59). This was later modified to include the tissue engineering as previously stated (2, 60). More recently, disinfection has been added as an integral and important part of the regenerative endodontic procedure protocol.

The AAE protocol lists the criteria for success for these REPs and divides this into primary, secondary and tertiary goals (Figure 7).

The majority of human case studies have shown high success rates and good clinical outcomes (absence of clinical signs and symptoms, radiographic evidence of resolution of periapical infections, continued root development and increased canal wall thickness) for immature permanent teeth with pulpal necrosis following REPs (19, 44, 46, 61-72). Analyses of radiographic and survival outcomes of immature teeth treated with either REPs or apexification found that significantly greater increases in root length and/or thickness following REPs in comparison to apexification procedures (56, 73, 74).

There is limited information on the exact histological nature of the tissue in the root canal following REPs in humans. However, recent reports describe the presence of pulp-like tissue in human teeth extracted following REPs (75-77). Conversely, other reports describe it as a combination of connective tissue, bone and cementum, or dentin and cementum, and not true pulpal tissue (78, 79). In dogs, the deposition of cementum-like and bone-like tissues was observed after REPs (80, 81), suggesting the ingrowth of periodontal ligament tissue versus actual regeneration of pulp tissue.

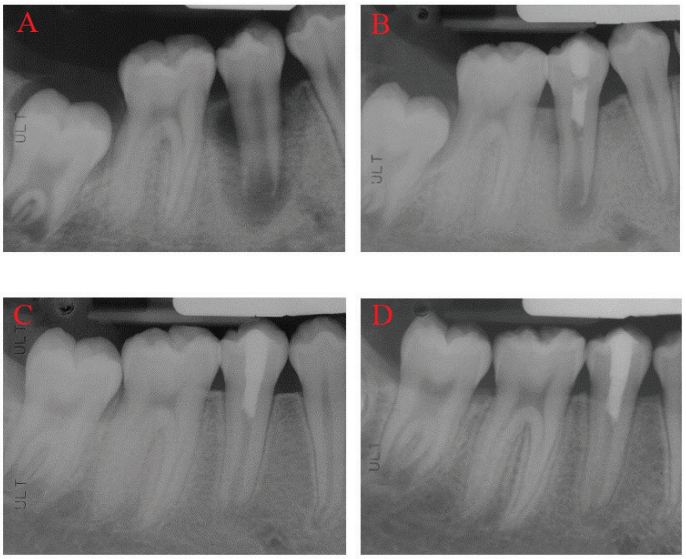


**Figure 6.** (A). Preoperative radiograph. The second premolar has an open apex with a large periradicular radiolucency. (B) Radiograph confirming the placement of MTA approximately 3 mm below the CEJ. The MTA was carefully placed over the blood clot, followed by a wet cotton pellet and Cavit. (C) Twelve-month radiograph showing continued root development. (D) Eighteen-month radiograph showing continued root development.

(From Banchs F, Trope M. Revascularization of immature permanent teeth with apical periodontitis: new treatment protocol? J Endod. 2004 Apr;30(4):196-200. doi: 10.1097/00004770-200404000-00003. PMID: 15085044.)

- Primary goal: The elimination of symptoms and the evidence of bony healing.
- Secondary goal: Increased root wall thickness and/or increased root length (desirable, but perhaps not essential)
- Tertiary goal: Positive response to vitality testing (which if achieved, could indicate a more organized vital pulp tissue)

**Figure 7.** Guidelines for clinical and radiographic follow-up evaluation after regenerative endodontic procedures.

A positive response to cold and/or electric pulp tests occurs in some cases (18, 19, 58, 64, 67, 82), but an absence of response does not indicate a lack of vitality (44). Radiographic evidence of apical healing typically precedes continuation of root development. It has been suggested that the extent of root development may depend on how well Hertwig's epithelial root sheath survives the infectious process (83). This may explain the radiographic appearance of teeth after REPs that remain asymptomatic and functional with complete periapical healing and apical closure, but minimal increase in root length, which is an outcome that should be considered acceptable (44).

Although the reported success rates of REPs are high, every procedure carries the possibility of failure. A few recent studies have discussed the failures associated with REPs and outlined the potential causes of failure. Outcomes of the REPs is largely dependent on the initial cause of pulp necrosis. (56, 84-86). The main causes of pulp necrosis have been attributed to trauma, developmental anomalies (such as dens

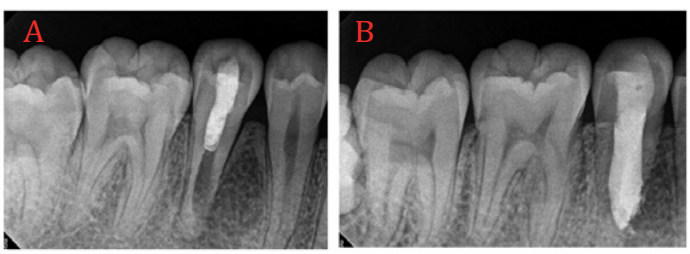


**Figure 8.** (A) 6- year post treatment evaluation radiograph of tooth #29 following regenerative endodontic treatment. Radiograph shows a large diffuse PA lesion; B. Tooth #29 treated with an apexification procedure after the failure of the regenerative endodontic procedures. (Courtesy of Dr. Tanner Neiman, Seattle, WA.)

evaginatus), followed by dental caries. The most failures were seen in trauma cases and these have required subsequent interventions like apexification, second REPs, NSRCT or extraction (Figure 8). Another important cause of failure has been attributed to inadequate disinfection (85, 87). Hence, considering the etiology of pulp necrosis and adequate disinfection could further improve the success rates of REPs.

## What could regenerative endodontics look like in the future?

Research is currently ongoing to develop new strategies to generate tissues that mimic the original pulp and dentin-like structure. These strategies include but are not limited to cell-based therapies that utilize autologous stem cells, customized scaffolds and delivery of appropriate growth factors which are delivered at the right time and in the right sequence, and methods to promote better and more potent disinfection. Further translational research is needed to learn about these processes and, importantly, ensure that new protocols are clinically practical.

It is evident that recent rapid advances have opened the door to exciting new opportunities in the quest for healing of immature teeth with pulpal necrosis. Extension of these advances are currently being used in the treatment of mature teeth with pulpal necrosis (47, 89, 90). These would provide significant therapeutic benefits by enabling retention of the natural dentition in a larger patient pool.

## Summary

Regenerative endodontics represents one of the most exciting advancements in modern dentistry, with endodontists leading the charge in this innovative research. By leveraging expertise in the field of pulp biology, dental trauma, and tissue engineering, researchers are pioneering biologically based treatments for mature and immature permanent teeth with pulpal necrosis. These regenerative procedures promote continued root development, enhanced dentinal wall thickness, and apical closure. The progress in regenerating a functional pulp-dentin complex holds significant potential in preserving natural teeth and aligns with the ultimate goal of endodontic care: maintaining the patient's natural dentition.

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