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Regenerative Endodontics: New-Age Concepts, Materials, and Clinical Applications - A Narrative Review

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Abstract

Regenerative endodontics represents a biologically driven paradigm shift in the management of teeth with compromised pulpal vitality, particularly immature permanent teeth with necrotic pulps. Conventional endodontic therapies successfully eliminate infection but result in loss of pulp vitality and cessation of root development, predisposing teeth to structural weakness and fracture. Regenerative endodontic procedures (REPs) aim to restore the pulp–dentin complex through biologically based strategies grounded in tissue engineering principles. These approaches integrate stem cells, bioactive scaffolds, and signaling molecules to promote cellular migration, differentiation, and tissue regeneration within the disinfected root canal system. Advances in biomaterials, platelet concentrates, stem cell biology, and cell-free regenerative strategies have expanded the clinical scope of regenerative endodontics beyond revascularization alone. However, variability in protocols, unpredictable clinical outcomes, and histological evidence of repair rather than true regeneration continue to limit widespread adoption. This narrative review synthesizes contemporary concepts, materials, and clinical applications of regenerative endodontics, highlighting emerging technologies and future directions aimed at achieving predictable and biologically authentic pulp–dentin regeneration.

Keywords: regenerative endodontics, pulp regeneration, tissue engineering, stem cells, scaffolds, biomaterials

Introduction

The preservation of pulp vitality is fundamental to maintaining tooth integrity, proprioception, immune defense, and long-term structural stability. Traditional endodontic procedures, including root canal therapy and apexification, effectively control infection but invariably result in a non-vital tooth lacking regenerative potential.

This limitation is particularly significant in immature permanent teeth, where incomplete root development, thin dentinal walls, and wide apical foramina increase susceptibility to fracture and long-term failure[1,2].

Regenerative endodontics emerged in response to these shortcomings, shifting therapeutic objectives from disinfection and obturation toward biological restoration of the pulp–dentin complex. Defined as biologically based procedures designed to replace damaged dentin, root structures, and cells of the pulp–dentin complex, regenerative endodontic therapy (RET) is grounded in tissue engineering principles[3]. Early clinical reports demonstrating continued root development following canal disinfection and induction of apical bleeding provided compelling evidence for the regenerative potential of immature teeth[4,5].

Over the past two decades, regenerative endodontics has gained increasing acceptance, supported by position statements from the American Association of Endodontists (AAE) and the European Society of Endodontology (ESE), which recognize REPs as a preferred treatment option for immature teeth with necrotic pulps under appropriate clinical conditions[6,7]. Despite promising clinical outcomes, challenges remain in achieving predictable regeneration and translating experimental advances into routine clinical practice.

Biological Basis of Regenerative Endodontics

Regenerative endodontics is founded on the tissue engineering triad comprising stem cells, scaffolds, and signaling molecules. The biological rationale involves creating a sterile and conducive microenvironment within the root canal system that enables endogenous or exogenous stem cells to migrate, proliferate, and differentiate into pulp-like tissue[8].

Immature teeth present a unique biological advantage due to the presence of the apical papilla, which contains stem cells of the apical papilla (SCAP). These cells exhibit high proliferative capacity and odontogenic potential, even in the presence of apical pathology[9]. Additionally, residual pulp tissue, periodontal ligament stem cells, and bone marrow-derived mesenchymal stem cells may contribute to regenerative outcomes through cell homing mechanisms [10].

Successful regeneration is critically dependent on effective disinfection while preserving stem cell viability. Excessive instrumentation or cytotoxic irrigants can compromise the regenerative microenvironment, underscoring the importance of minimally invasive protocols[11].

Stem Cells in Regenerative Endodontics

Stem cells play a central role in pulp–dentin regeneration. Various dental and non-dental stem cell populations have been investigated, including dental pulp stem cells (DPSCs), SCAP, periodontal ligament stem cells, and mesenchymal stem cells derived from bone marrow or umbilical cord tissue[12,13,14].

Among these, SCAP are considered particularly advantageous due to their proximity to the root canal system and resistance to infection-associated inflammatory conditions[9]. Clinical and experimental studies have demonstrated that these cells can differentiate into odontoblast-like cells and contribute to dentin deposition and root maturation[15].

Cell-based regenerative approaches involving stem cell transplantation have shown encouraging results in experimental and early clinical trials; however, their clinical application is limited by ethical concerns, regulatory challenges, cost, and technical complexity[16,17]. Consequently, current clinical practice primarily relies on cell-free approaches that harness endogenous stem cell recruitment.

Scaffolds and Biomaterials

Scaffolds provide a three-dimensional framework that supports cell attachment, migration, and differentiation while facilitating the controlled release of bioactive molecules. The simplest and most widely used scaffold in regenerative endodontics is the blood clot formed following induced intracanal bleeding[18]. Blood clots serve as a natural scaffold rich in fibrin and growth factors but are associated with variability in stability and regenerative outcomes.

To overcome these limitations, platelet concentrates such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have been introduced. These biomaterials provide higher concentrations of growth factors and improved scaffold stability, with several studies reporting enhanced root development and periapical healing compared to traditional blood clot techniques [19,20].

Advances in biomaterials science have led to the development of synthetic and naturally derived scaffolds, including collagen matrices, hydrogels, and bioactive ceramics. Emerging technologies such as three-dimensional bioprinting enable the fabrication of customized scaffolds that mimic the native pulp architecture, improving cell organization and nutrient diffusion[21].

Signaling Molecules and Growth Factors

Signaling molecules regulate cellular behavior by directing migration, proliferation, angiogenesis, and differentiation. Growth factors embedded within dentin matrices, such as transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and fibroblast growth factors, can be released during irrigation and scaffold placement, contributing to regenerative processes[22].

Chemotactic molecules such as stromal cell-derived factor-1 (SDF-1) and Wnt signaling proteins have demonstrated significant potential in promoting stem cell homing and neurovascular regeneration within the canal space[23]. Additionally, emerging interest in exosome-based therapies highlights their role in intercellular communication and immunomodulation, offering a promising cell-free regenerative strategy[24].

Clinical Protocols and Applications

Current regenerative endodontic protocols emphasize minimal mechanical instrumentation, copious irrigation with low-concentration sodium hypochlorite, and the use of intracanal medicaments to eliminate infection while preserving stem cell viability [6,11]. Antibiotic pastes or calcium hydroxide are commonly employed, followed by induction of intracanal bleeding to create a scaffold for regeneration.

A biocompatible coronal seal, typically achieved using mineral trioxide aggregate or bioceramic materials, is essential to prevent reinfection and ensure a favorable healing environment[25]. Clinical success is primarily defined by resolution of symptoms and periapical healing, with secondary outcomes including increased root length, dentinal wall thickening, and apical closure[26]. While REPs were initially limited to immature teeth, recent reports suggest potential applications in mature teeth under specific conditions, although outcomes remain less predictable[27].

AAE Clinical Considerations for a Regenerative Procedure Revised November 2022

Case Selection:[28]

1. Tooth with necrotic pulp and an immature apex.
2. Pulp space not needed for post/core, final restoration.
3. Compliant patient/parent.
4. Patients not allergic to medicaments and antibiotics necessary to complete procedure (ASA 1 or 2).

Informed Consent

1. Two (or more) appointments.
2. Use of antimicrobial(s).
3. Possible adverse effects: staining of crown/root, lack of response to treatment, pain/infection.
4. Alternatives: MTA apexification, no treatment, extraction (when deemed non salvageable).

First Appointment

1. Local anesthesia, dental dam isolation and access.
2. Copious, gentle irrigation with 20ml NaOCl using an irrigation system that minimizes the possibility of extrusion of irrigants into the periapical space (e.g., needle with closed end and side-vents, or EndoVac™). Lower concentrations of NaOCl are advised [1.5%-3% NaOCl (20mL/canal, 5 min) and then irrigated with saline or EDTA (20 mL/canal, 5 min), with irrigating needle positioned about 1 mm from root end, to minimize cytotoxicity to stem cells in the apical tissues.
3. Dry canals with paper points.

➢ Place calcium hydroxide or low concentration of triple antibiotic paste. If the triple antibiotic paste is used:

A. Consider sealing pulp chamber with a dentin bonding agent [to minimize risk of staining]

B. Mix 1:1:1 ciprofloxacin: metronidazole: minocycline to a final concentration of 1-5 mg/ml. Triple antibiotic paste has been associated with tooth discoloration. Double antibiotic paste without minocycline paste or substitution of minocycline for other antibiotic (e.g., clindamycin; amoxicillin; cefaclor) is another possible alternative as root canal disinfectant. Clinicians should be aware that studies have been done using higher concentrations of TAP/DAP, but a recommendation to a higher concentration can't be made at this time due to limited studies.

4. Deliver into canal system via syringe
5. If triple antibiotic is used, ensure that it remains below CEJ (minimize crown staining).
6. Seal with 3-4mm of a temporary restorative material such as Cavit™, IRM™, glass ionomer or another temporary material. Dismiss patient for 1-4 weeks.

Second Appointment (1-4 weeks after 1st visit)

1. Assess response to initial treatment. If there are signs/symptoms of persistent infection, consider additional treatment time with antimicrobial, or alternative antimicrobial.
2. Anesthesia with 3% mepivacaine without vasoconstrictor, dental dam isolation.
3. Copious, gentle irrigation with 20ml of 17% EDTA.
4. Dry with paper points.
5. Create bleeding into canal system by over-instrumenting (endo file, endo explorer) (induce by rotating a pre-curved K-file at 2 mm past the apical foramen with the goal of having the entire canal filled with blood to the level of the cemento–enamel junction). An alternative to creating of a blood clot is the use of platelet-rich plasma (PRP), platelet rich fibrin (PRF) or autologous fibrin matrix (AFM).
6. Stop bleeding at a level that allows for 3-4 mm of restorative material.

- Place a resorbable matrix such as CollaPlug™, Collacote™, CollaTape™ over the blood clot if necessary and white MTA as capping material.
- A 3–4 mm layer of glass ionomer (e.g. Fuji IX™, GC America, Alsip, IL) is flowed gently over the capping material and light-cured for 40 s. MTA has been associated with discoloration. Alternatives to MTA (such as bioceramics or tricalcium silicate cements [e.g., Biodentine®, Septodont, Lancasted, PA, USA,

EndoSequence® BC RRM-Fast Set Putty, Brasseler, USA]) should be considered in teeth where there is an esthetic concern.

- Anterior and Premolar teeth - Consider use of Collatape/Collaplug and restoring with 3mm of a nonstaining restorative material followed by bonding a filled composite to the beveled enamel margin.
- Molar teeth or teeth with PFM crown - Consider use of Collatape/Collaplug and restoring with 3mm of MTA, followed by RMGI, composite or alloy.

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

1. 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

2. The degree of success of Regenerative Endodontic Procedures is largely measured by the extent to which it is possible to attain primary, secondary, and tertiary goals:

- 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)

Outcomes, Limitations, and Complications

Clinical studies consistently report high rates of symptom resolution and periapical healing following regenerative endodontic therapy. However, continued root development and recovery of pulp sensibility are variable and unpredictable [26,29].

Histological evidence indicates that tissues formed within the canal space often resemble periodontal connective tissue rather than true pulp tissue, suggesting that repair predominates over genuine regeneration[30]. Complications such as crown discoloration, canal obliteration, and inconsistent sensibility responses further highlight the need for protocol refinement[31].

Future Directions and Emerging Technologies

Future advances in regenerative endodontics are expected to focus on improving biological predictability through gene therapy, advanced scaffold design, and immunomodulatory biomaterials. Gene-based delivery of growth factors may enable precise control of cellular differentiation, while cell-free approaches utilizing bioactive scaffolds and exosomes offer simplified and clinically feasible alternatives to stem cell transplantation[21,24].

The development of standardized clinical protocols and outcome measures will be essential for translating regenerative endodontics from an experimental modality into routine clinical practice.

Conclusion

Regenerative endodontics represents a transformative approach that extends beyond infection control to biologically restore the pulp–dentin complex. While current clinical protocols achieve favorable healing outcomes, true pulp regeneration remains an aspirational goal. Continued advancements in biomaterials, signaling strategies, and translational research are essential to realize the full potential of regenerative endodontic therapy.

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