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REVIEW ARTICLE

Regenerative Endodontics: Current Concepts, Clinical Protocols, and Future Directions

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ABSTRACT

Regenerative endodontics is a paradigm shift in the treatment of immature permanent teeth with necrotic pulps that uses beyond apexification methods, biologically-based methods that repair the pulp-dentin complex. The recent theories have focused on the three components of tissue engineering that include stem cells, scaffolds, and signaling molecules and the importance of the apical papilla in the maturation and healing of roots. Standardized clinical protocols are currently based on conservative canal disinfection, the induction of a biological scaffold (platelet concentrates or blood clots), and bioactive material sealing. Even though good results have been obtained, such as periapical healing, increased root wall thickness, and sustained root growth, shortcomings remain with respect to the predictability of genuine regeneration of the pulp, the potential of tooth discoloration, and inconsistent responses of long-term vitality. Continued developments in biomaterials, gene therapy, stem cell therapies and nanotechnology have the potential to eliminate these challenges and make regenerative endodontics more clinically applicable.. Future directions aim toward predictable, personalized, and biologically driven treatment strategies that may redefine the standard of care in endodontics.

Keywords: Regenerative endodontics, tissue engineering, stem cells, scaffolds, pulp–dentin complex, clinical protocols, bioactive materials.

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Introduction

Eradication of infection and maintenance of the natural dentition is regarded as the key goal of endodontic treatment. Traditional methods like calcium hydroxide apexification or mineral trioxide aggregate (MTA) apical barrier methods have traditionally given a solution to periapical pathology but not maturation of the root in immature permanent teeth with necrotic pulp. As a result, these teeth tend to be weak, and the walls of the dentin are thin, and they are easily fractured.

Regenerative endodontics refers to a biologically conceptualized treatment modality, which aims at the restoration of a functional pulp-dentin complex and enhancement of root growth. This treatment idea is based on the theory of tissue engineering, where the stem cells, scaffolds, and signaling molecules are used to promote repair and regeneration. Initial experimental and clinical research have shown that periapical disease, thickening of dentinal walls and restoration of pulp vitality in immature teeth can be resolved.

Clinical protocols and outcome measures have since been offered by American Association of Endodontists (AAE) and other bodies around the world to standardize practice and make practice reducible. Although these have been made, a number of challenges that still abound include variable response of treatment, lack of certainty about the nature of the regenerated tissue and requirement of long-term clinical validation.

This is a review of the current notions of regenerative endodontics, the present day clinical protocols, challenges and limitations and future prospects of endodontic regeneration to attain predictability and biology-driven regeneration.

Current Concepts

Regenerative endodontics is grounded in the principles of tissue engineering, which integrate stem cells, scaffolds, and signaling molecules to facilitate repair and regeneration of

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the pulp–dentin complex. Unlike conventional endodontic procedures that focus primarily on disinfection and obturation, regenerative strategies aim to reestablish vital tissue within the root canal space, thereby preserving tooth function and enabling continued root development.

A key biological basis for regenerative therapy is the presence of stem cells of the apical papilla (SCAP), periodontal ligament stem cells, and other progenitor cell populations capable of differentiating into odontoblast-like cells. These cells contribute to dentinogenesis and play a central role in promoting root elongation and apical closure in immature teeth. The apical region also provides a natural source of growth factors that can be released during canal irrigation and scaffold placement, further supporting cellular activity and tissue regeneration.

Scaffold systems serve as a three-dimensional framework for cell migration, proliferation, and differentiation. Traditionally, the induced blood clot has been employed as a natural scaffold; however, biologically enriched alternatives such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have gained prominence for their higher concentrations of growth factors and improved handling properties. Concurrently, bioactive materials such as mineral trioxide aggregate (MTA) and Biodentine are used as coronal barriers, offering both biocompatibility and sealing ability.

The release of endogenous signaling molecules, including transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF), is also fundamental to regenerative processes. These factors stimulate angiogenesis, neurogenesis, and dentin–pulp complex regeneration, thereby enhancing the potential for functional restoration rather than mere repair.

Current success criteria extend beyond radiographic evidence of apical closure and periapical healing to include clinical signs of vitality, increased root wall thickness, and absence of reinfection. Nevertheless, variability in outcomes has highlighted the complexity of true pulp regeneration and emphasized the need for more standardized treatment protocols and biologically guided interventions.

Clinical Protocols

The clinical application of regenerative endodontics has evolved considerably, with efforts directed toward developing standardized, reproducible, and biologically based procedures. While variations exist among clinicians and research groups, the following steps represent the consensus guidelines and widely accepted protocols endorsed by leading endodontic organizations.

Case Selection and Indications

Successful regenerative endodontic procedures (REPs) depend heavily on proper case selection. Indicated cases include immature permanent teeth with:

- Pulpal necrosis or irreversible pulpitis, often secondary to trauma or caries.
- Incomplete root development with open apices.
- Absence of extensive root fractures or severe periodontal compromise.

Contraindications include teeth with insufficient apical papilla, advanced root resorption, or lack of patient compliance.

First Appointment: Disinfection and Temporary Sealing

Access and minimal instrumentation

The canal system is accessed, and instrumentation is minimized to preserve stem cells in the apical papilla. Mechanical debridement is avoided or kept to a minimum.

Irrigation protocol

Irrigation with 1.5% sodium hypochlorite (NaOCl) is recommended, followed by 17% ethylenediaminetetraacetic acid (EDTA). This combination disinfects the canal while preserving dentin-derived growth factors. High concentrations of NaOCl should be avoided to reduce cytotoxicity to stem cells.

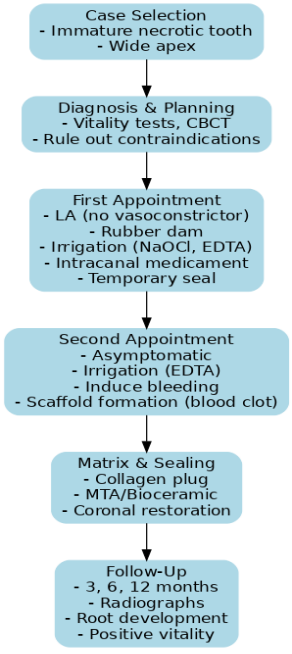

Fig 1: The diagram is a graphical flowchart of the clinical protocols in Regenerative Endodontics.

Intracanal medicaments

Triple antibiotic paste (TAP: ciprofloxacin, metronidazole, minocycline) or double antibiotic paste (ciprofloxacin, metronidazole) is traditionally used, though calcium hydroxide is also effective and minimizes discoloration risk. The medicament is placed short of the apex and sealed coronally with a temporary restorative material for 2–4 weeks.

Second Appointment: Scaffold Induction and Coronal Seal

Assessment

Absence of signs and symptoms (pain, swelling, sinus tract) and resolution of infection must be confirmed before proceeding.

Scaffold creation

After irrigation with saline or EDTA, periapical bleeding is induced by overinstrumentation with a sterile endodontic file to a few millimeters beyond the apical foramen. This bleeding introduces mesenchymal stem cells from the apical papilla into the canal space, forming a blood clot scaffold. Alternatives include platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), which provide a concentrated supply of growth factors.

Barrier placement

Once the scaffold reaches 2–3 mm below the cementoenamel junction, a resorbable matrix (e.g., CollaPlug) may be used as a barrier. Over this, a bioceramic material such as mineral trioxide aggregate (MTA), Biodentine, or calcium silicate–based cements is placed to seal the canal and prevent bacterial leakage.

Coronal restoration

A bonded permanent restoration (e.g., composite resin) is placed to ensure a hermetic seal, essential for long-term success.

Follow-Up and Outcome Assessment

Clinical evaluation

Periodic assessment at 3, 6, and 12 months is essential, with continued annual monitoring. Clinical signs of success include absence of pain, swelling, or sinus tract, and restoration of tooth function.

Radiographic evaluation

Desired outcomes include resolution of periapical radiolucency, continued root maturation (apical closure, increase in root length and wall thickness), and in some cases, pulp vitality response to sensibility tests.

Outcome variability

While periapical healing and root development are common, pulp vitality and true regeneration of pulp–dentin complex remain inconsistent. Calcific tissue deposition and canal obliteration may occur, reflecting repair rather than complete regeneration.

Modifications and Standardization Efforts

Recent refinements include the use of lower concentrations of NaOCl, avoidance of minocycline to prevent staining, and introduction of bioactive scaffolds enriched with growth factors. Professional organizations, including the American Association of Endodontists (AAE) and the American Academy of Pediatric Dentistry (AAPD), have emphasized evidence-based protocols to improve consistency and predictability.

Challenges and Limitations

Despite the significant progress in regenerative endodontics, several challenges and limitations continue to hinder its predictable clinical application. These issues relate to biological, clinical, and translational factors that require careful consideration.

Biological uncertainty

One of the major limitations is the lack of clarity regarding the true nature of the regenerated tissue. Histological studies often reveal the formation of cementum-like, bone-like, or fibrous connective tissue rather than functional pulp tissue. This raises concerns about whether current procedures achieve genuine regeneration of the pulp–dentin complex or merely repair through tissue replacement.

Variability in clinical outcomes

Clinical outcomes of regenerative procedures remain inconsistent. While some cases demonstrate resolution of symptoms, apical closure, and continued root development, others show limited or no root maturation. Factors such as patient age, extent of apical papilla vitality, pre-existing infection, and procedural variations contribute to this variability.

Risk of tooth discoloration

The use of intracanal medicaments such as triple antibiotic paste (especially minocycline) and certain bioactive materials like mineral trioxide aggregate (MTA) can result in coronal discoloration. This esthetic concern poses a

particular challenge in anterior teeth and necessitates alternative materials or modified protocols.

Infection Control and Reinfection Risk

Achieving complete canal disinfection without damaging periapical stem cells is complex. Aggressive irrigation may impair stem cell viability, whereas insufficient disinfection increases the risk of reinfection and treatment failure. The delicate balance between microbial control and preservation of the regenerative microenvironment remains a clinical challenge.

Pulp canal obliteration and calcification

Cases of intracanal calcification and pulp canal obliteration have been reported following regenerative procedures. These outcomes, while compatible with periapical healing, may compromise future retreatment and devitalize the tooth structurally without restoring true pulp vitality.

Lack of standardization

Although clinical guidelines exist, protocols for disinfection, scaffold induction, and material selection vary widely among practitioners and studies. This lack of standardization complicates the evaluation of treatment success and hinders the development of universally accepted protocols.

Limited long-term evidence

Most available data are based on short- to medium-term clinical outcomes. Long-term evidence demonstrating sustained vitality, functional pulp regeneration, and predictable success is still limited, highlighting the need for robust clinical trials and histological validation.

Summary Box on the Key Challenges and Limitations in Regenerative Endodontics

- Ambiguity regarding true pulp regeneration versus repair
- Inconsistent clinical outcomes influenced by patient- and technique-related factors
- Tooth discoloration associated with certain medicaments and materials
- Difficulty balancing effective disinfection with preservation of stem cells
- Incidence of canal obliteration and calcification
- Variability and lack of standardized clinical protocols
- Limited availability of long-term, evidence-based data

Future Directions

Regenerative endodontics is rapidly evolving, and several emerging strategies aim to overcome current challenges and enhance clinical predictability. The future of the field lies in integrating advanced biomaterials, biological therapies, and precision approaches tailored to individual patient needs.

Advanced scaffolds and biomaterial

Next-generation scaffolds, including injectable hydrogels, bioengineered matrices, and nanostructured materials, are being developed to provide a controlled microenvironment for cell proliferation and differentiation. These materials may allow for better vascularization and integration of the regenerated pulp tissue.

Stem cell - based therapies

While current protocols rely mainly on the recruitment of endogenous stem cells, future approaches may incorporate exogenous stem cell transplantation derived from sources such as dental pulp stem cells, stem cells from apical papilla, or induced pluripotent stem cells. This strategy holds the potential for more predictable tissue regeneration and functional pulp restoration.

Gene therapy and bioactive molecules

The use of bioactive molecules, such as growth factors and cytokines, is being explored to direct stem cell behavior and promote dentin–pulp complex regeneration. Gene therapy approaches may further enhance this by modulating cellular pathways that control angiogenesis, neurogenesis, and odontoblast differentiation.

Immunomodulation and host response

Emerging evidence highlights the importance of immune regulation in tissue healing. Strategies aimed at modulating the host immune response may improve stem cell survival, reduce inflammation, and foster a more favorable regenerative environment.

Three-dimensional bioprinting and tissue engineering

3D bioprinting technologies are being investigated for the fabrication of customized pulp-like tissue constructs. By combining patient-derived cells with bioengineered scaffolds, this approach could pave the way for personalized regenerative therapies with high clinical precision.

Digital and personalized endodontics

Advances in digital imaging, artificial intelligence, and predictive modeling may support patient-specific treatment planning and risk assessment. Personalized regenerative endodontics could ensure optimized protocols tailored to the biological and clinical characteristics of each case.

Translational and clinical research

Large-scale, long-term clinical trials and multicenter studies are essential to establish standardized protocols and

validate regenerative approaches. Bridging the gap between laboratory discoveries and clinical implementation will be crucial for widespread adoption.

Conclusion

Regenerative endodontics is an innovative treatment that changes the normal approach of apexification and obturation to biologically-driven approaches that focus on restoring the pulp-dentin complex. The existing guidelines, which are also based on the principles of tissue engineering, have demonstrated sufficiently positive clinical results, such as the healing of periapical areas, the maturation of roots, and maintenance of the functionality of teeth. Nonetheless, some of the limitations that include variability in the results, discoloration risk, and an inability to understand the actual nature of the regenerated tissues indicate the necessity of refinement/standardization.

It is anticipated that with the development of scaffolds, stem cell biology, bioactive molecules, and immunomodulation, combined with the incorporation of digital technologies and personalized medicine, predictability and the overall success of regenerative procedures will be improved significantly. To prove these innovations and make regenerative endodontics a viable and popular form of treatment, future research and strong clinical trials will be necessary to further development and translation of the findings to a broader audience. Eventually, the vision is to reach stable, biologically motivated, and patient-centered results that will transform the future of care in the endodontic field.

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