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# Regenerative Endodontics in Children: Current Evidence, Challenges, and Future Directions

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## ABSTRACT

**The management of immature permanent teeth with necrotic pulps presents a significant challenge in paediatric endodontics, due to incomplete root formation, thin dentinal walls, and vulnerability to fracture. Traditional methods (e.g., apexification) promote apical closure but do not restore the functional pulp–dentin complex or allow for continued root maturation. Regenerative endodontic procedures (REPs) represent a paradigm-shift, aiming to biologically regenerate pulpal tissue, reestablish the pulp–dentin complex, and promote root development. This review critically examines the current evidence for REPs in children, discusses the biological basis and clinical protocols, highlights specific issues in the paediatric population, identifies current limitations and challenges, and outlines future directions. Although REPs demonstrate promising clinical and radiographic outcomes (resolution of apical periodontitis, increased root length and width), histologic evidence of true pulp–dentin regeneration remains limited. Standardised protocols, outcome definitions, longer-term follow-up data, and translational research are needed before REPs can be considered as routine therapy in paediatric endodontics.**

**Keywords: regenerative endodontics; immature permanent teeth; paediatric endodontics; stem cells; pulp regeneration; root maturation.**

## INTRODUCTION

Teeth with incomplete root development (immature permanent teeth) are particularly prone to pulp necrosis following trauma or extensive caries, largely because of the immature anatomy: large apical foramina, thin dentinal walls, and wide canals. Without the protective and nutritive function of the pulp, root maturation arrests, leaving the tooth with thin roots, poor crown-to-root ratio, and increased fracture risk [1,2]. Traditional management has relied on apexification procedures (e.g., long-term calcium hydroxide or one-step mineral trioxide aggregate [MTA] apical plugs) to induce apical closure. However, these techniques do not restore vitality, nor do they reliably promote continued root wall thickening or increased root length [3].

The concept of regenerative endodontics emerged to address these limitations, aiming to replace damaged pulp tissue with viable tissue capable of continuing root maturation and ideally regenerating a functional pulp–dentin complex [4]. Initial successful case reports in the early 2000s (e.g., Iwaya et al. 2001; Banchs & Trope 2004) sparked significant interest [5,6]. More recently, guidance documents from the American Association of Endodontists (AAE) and the European Society of Endodontology (ESE) have formalised indications and protocols [7]. For paediatric practitioners, the intersection of pedodontics and endodontics is particularly relevant—children frequently present with immature teeth after trauma or deep caries, and successful biologic regeneration could dramatically improve outcomes. Yet, the evidence base remains evolving. This review focuses on children and immature permanent teeth, exploring the biological basis, clinical evidence, special paediatric considerations, challenges, and future directions of REPs.

### Biological Basis of Regenerative Endodontics

### The tissue engineering triad

Regenerative endodontic procedures are founded on the triad of stem/progenitor cells, scaffolds, and signalling molecules/growth factors (bioactive cues) [4,8] (Figure 1).

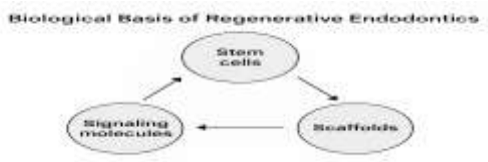


**Figure 1. Biological basis of regenerative endodontics illustrating the tissue-engineering triad-stem cells, scaffolds, and signaling molecules-interacting synergistically to achieve pulp–dentin regeneration.**

**Stem/progenitor cells:** Multiple sources are implicated in root canal regeneration: dental pulp stem cells (DPSCs), stem cells from the apical papilla (SCAP), and stem cells from human exfoliated deciduous teeth (SHED). SCAP cells are particularly relevant in immature teeth because they are located apically, are mitotically active, and play a key role in continued root formation [9]. DPSCs likewise have odontoblastic potential. SHED are more pertinent for regenerative use but less common clinically in endodontic practice.

**Scaffolds:** A scaffold is required to allow cell migration, proliferation and differentiation. In clinical REPs, the scaffold is often the induced blood clot, platelet-rich plasma (PRP) or platelet-rich fibrin (PRF), or synthetic scaffolds (hydrogels, collagen, chitosan matrices) in experimental settings [8,10]. The blood clot provides a natural matrix rich in cellular components and growth factors.

**Signalling molecules/growth factors:** Growth factors such as bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and platelet-derived growth factor (PDGF) regulate angiogenesis, odontoblastic differentiation, and pulp tissue regeneration [4].

**Mechanism of action**

In the typical REP, after root canal disinfection, bleeding is induced by over-instrumentation or stimulating periapical tissues, producing a blood clot scaffold that carries stem/progenitor cells and growth factors into the canal space. The subsequent deposition of tissue and hard tissue along the canal walls may lead to thickening of dentinal walls and continued root lengthening [3,8]. The ultimate goal is regeneration of a pulp–dentin complex with innervation, vascular supply, and odontoblastic layer—but in practice, much of the outcome may instead be repair tissue (cementum or bone-like) rather than true pulp [8].

**Clinical Protocols and Current Evidence**

**Disinfection methods**

Effective disinfection of the root canal space while preserving the viability of surrounding stem cells is a critical first step in REPs. The AAE guidelines recommend gentle irrigation (e.g., 1.5–3 % NaOCl with minimal extrusion, followed by 17 % EDTA) and intracanal medicaments [7]. Historically, the tri-antibiotic paste (metronidazole, ciprofloxacin, minocycline) has been used, but concerns include cytotoxicity to stem cells, crown discoloration (minocycline) and bacterial resistance [3,11]. Alternatives include double-antibiotic pastes (minocycline omitted) or calcium hydroxide, which may have less cytotoxicity but perhaps less antimicrobial efficacy [3]. Recent reviews emphasise that canal disinfection and an aseptic environment are more important than the precise medicament chosen [3] (Figure 2).

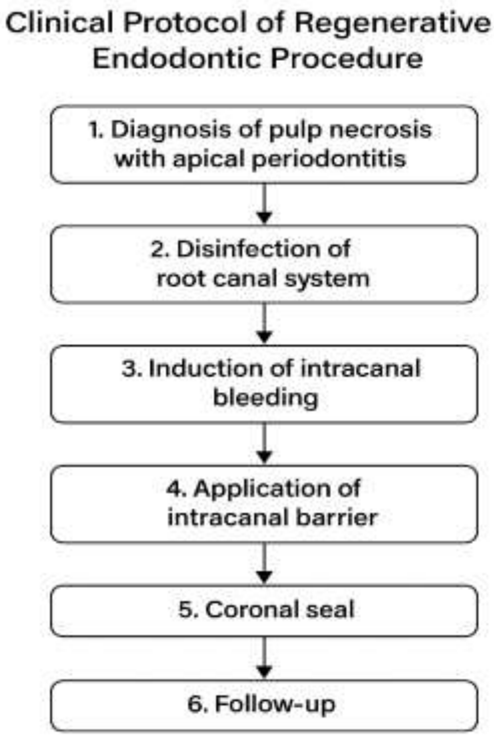


**Figure 2. Clinical protocol of regenerative endodontic procedure depicting the sequential stages: (1) diagnosis of pulp necrosis with apical periodontitis, (2) root canal disinfection, (3) induction of intracanal bleeding, (4) placement of intracanal barrier, (5) coronal sealing, and (6) follow-up evaluation.**

### Scaffold induction and coronal seal

Following disinfection and medicament placement, the next step is scaffold induction. At the second appointment (typically after 2–4 weeks, when symptoms resolve), the medicament is removed, the canal is irrigated with EDTA to promote growth factor release from dentin, then bleeding is induced (via file or apex irritant) to allow stem/progenitor cells migration [7,12]. A biocompatible barrier (e.g., MTA, Biodentine) is placed over the clot, followed by coronal restoration [7]. The quality of the scaffold/clot (height and extent), effective apical bleeding, and thorough coronal seal are all contributors to success [8].

### Clinical and radiographic outcomes

Outcome measures for REPs have evolved but typically include: (i) resolution of clinical signs and symptoms (pain, swelling, sinus tracts); (ii) radiographic evidence of root maturation (increased root length, increased root wall thickness, apical closure); and (iii) ideally, return of sensitivity/innervation [8]. Kim et al. reported that while clinical and radiographic success is relatively high, true regeneration (neurovascular pulp–dentin complex) is rarely achieved and histologic proof is sparse [8].

In one retrospective study comparing REPs vs apexification in immature teeth, REPs resulted in significantly greater increases in root width (28.2 %) and root length (14.9 %) compared to MTA apexification (0 % and 6.1 %) and calcium hydroxide apexification (1.5 % and 0.4 %) respectively [3]. More recent analyses note favourable outcomes in case reports and series, but emphasise heterogeneity in protocols and follow-up durations [12,13].

Meta-analysis is limited, but a 2021 review found that while resolution of apical radiolucency is common, continued root maturation is inconsistent and outcomes vary widely [4].

## Regenerative Endodontics in the Paediatric Population

### Patient selection

In children, the typical scenario for REP is an immature permanent tooth with necrotic pulp (often post-trauma or deep caries) and open apex. The consensus is that teeth with wide open apices (e.g., > 1 mm) and thin root walls are the ideal candidates [3,12]. Teeth with extensive crown destruction, horizontal root fractures, severe resorption, or patients with poor compliance may be less ideal.

### Age-related biological considerations

Younger patients may have enhanced regenerative potential owing to higher numbers and viability of stem/progenitor cells, more robust vascular supply, and overall growth capacity. The apical papilla in immature teeth contains SCAP cells, which may still be vital in children and adolescents [9]. Additionally, the use of SHED (stem cells from exfoliated deciduous teeth) presents a potential autologous source in paediatric cases, though clinical applications remain experimental.

In children, especially pre-adolescents, treatment planning must consider growth, eruption of adjacent teeth, and potential interaction with developing dentoalveolar structures. While REPs are not indicated for deciduous teeth (risk of interfering with eruption), in permanent immature teeth they provide a unique opportunity [3].

### Comparison with conventional therapy in children

While apexification (calcium hydroxide or MTA plug) remains a valid option, it has drawbacks: prolonged treatment, multiple visits, increased risk of root fracture due to long-term CH usage, and lack of further root development [3]. REPs offer the promise of continued root formation and thickening of dentinal walls, thereby potentially improving long-term prognosis in children whose teeth will be subjected to decades of functional load [3,4]. However, as emphasised earlier, evidence remains variable; thus in children, careful case selection and realistic expectations are critical.

## Current Challenges and Limitations

Despite the promise of REPs, several key limitations must be recognised.

**Lack of standardised protocols.** There is considerable heterogeneity in disinfection regimens, scaffold choice (blood clot vs PRP/PRF vs synthetic), use of MTA vs other capping materials, timing and follow-up intervals. This makes pooling of data and systematic comparison difficult [12,13].

**Unpredictable histologic outcomes:** Histologic investigations of teeth treated with REPs often reveal tissue types other than pulp–dentin complex (cementum-only, bone-like) and absence of true neurovascular pulp restoration [8]. Thus, many treatments may represent repair rather than true regeneration.

**Limited long-term data:** Many reports are case reports or short-term series (12-24 months). Long-term survival, functional outcomes, tooth strength/fracture resistance in children remain under-studied.

**Operator sensitivity and patient compliance:** The technique demands meticulous execution, bleeding induction is sometimes unpredictable, young patients may find multiple visits challenging, and coronal seal must be impeccable.

**Ethical and practical barriers for cell-based therapies:** While the potential for autologous stem cell transplantation or exosome therapies exists, in children this raises ethical issues, cost constraints, regulatory hurdles, and logistic challenges.

**Outcome measure ambiguity:** There is ongoing debate over how to define "success" — is apical closure sufficient, or does restoration of nerve sensitivity and pulp vitality matter? In paediatric practice, functional longevity and fracture risk prevention may be more relevant than traditional endodontic success metrics.

**Adoption in paediatric practice:** Recent survey work identified barriers to broader use of REPs: insufficient training, lack of conviction in outcomes, patient/parental reluctance, and variation in protocols between endodontists and paediatric dentists [14].

**Future Directions**

Regenerative endodontics is rapidly evolving. Several future directions are worth highlighting.

**Cell-based and cell-free therapies:** Beyond the blood-clot scaffold, research is increasingly focusing on engineered scaffolds incorporating stem cells (e.g., DPSCs, SCAP, SHED), and cell-free approaches (exosomes, growth factor-loaded biomaterials) [10]. These may improve the predictability of outcomes and reduce dependency on induced bleeding.

**3D bioprinting and nanoscaffold engineering:** Advanced scaffold fabrication (3D printed templates, nanofiber meshes with embedded growth factors) may enhance cell guidance, vascularisation, and tissue organisation within the root canal [8].

**Smart biomaterials and controlled growth factor delivery:** Biomaterials that release growth factors in a controlled manner (e.g., BMP-2, VEGF) and incorporate antimicrobial and bioactive properties may improve regeneration while maintaining disinfection [10].

**Digital dentistry integration and AI modelling:** Integration of digital imaging, CBCT, intra-oral scanners and AI-based predictive models may help in case-selection, root growth measurement, and outcome prediction in children undergoing REPs [8].

**Long-term clinical trials and standardized outcome metrics:** Paediatric-specific trials with longer follow-up (5-10 years) are needed, with standardized definitions of root development, tooth survival/fracture rate, patient-centred outcomes (pain, quality of life) and cost-effectiveness analyses.

**Personalised regenerative endodontics:** With advances in genomics and stem cell biology, personalised approaches (e.g., patient-specific stem cell sources, customised scaffolds) may become feasible. For children, where lifespan of the tooth is long, the concept of a biologically "living tooth" is appealing.

## CONCLUSIONS

Regenerative endodontics offers a transformative opportunity in paediatric endodontics: to move beyond artificial apical barriers toward biologically revitalised pulp–dentin complexes and continued root maturation. In children with immature permanent teeth, REPs may provide an avenue for improved long-term prognosis, enhanced root strength, and preservation of natural dentition. However, despite encouraging clinical and radiographic outcomes, many uncertainties remain: the nature of the regenerated tissue, long-term tooth survival and fracture resistance, standardisation of protocols, and broad clinical adoption. As paediatric and endodontic practitioners, we must apply REPs thoughtfully—ensuring rigorous case selection, informed consent (especially with parents/guardians), meticulous technique, and careful follow-up. Ongoing research will clarify their place in routine practice, but for now, REPs represent a promising, biologically inspired option worth considering in carefully selected cases.

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