Regenerative endodontics

applied sciences

MDPI

Review

Regenerative Endodontics as the Future Treatment of Immature Permanent Teeth

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applied sciences

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Review

Different Approaches to the Regeneration of Dental Tissues in Regenerative Endodontics

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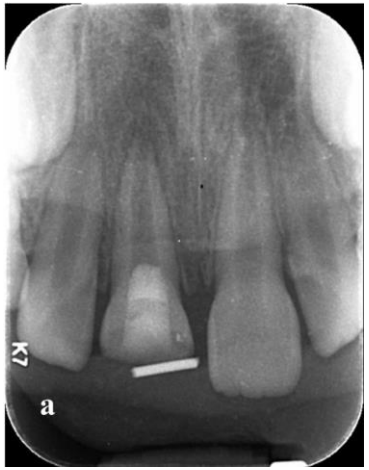
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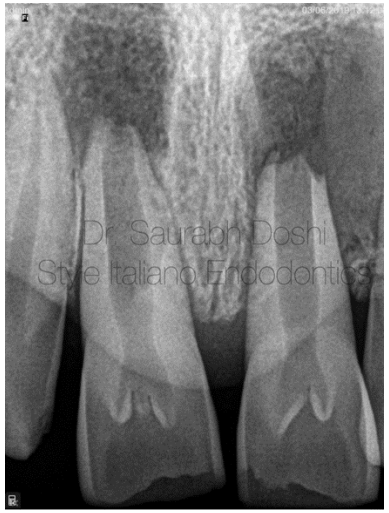
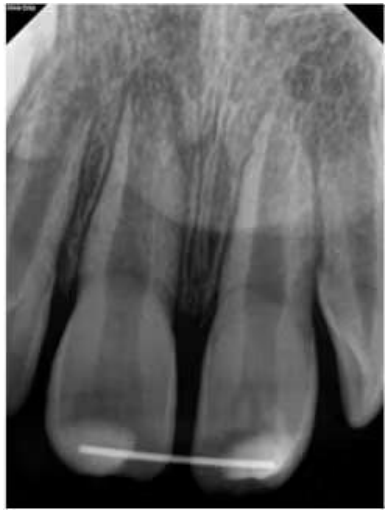
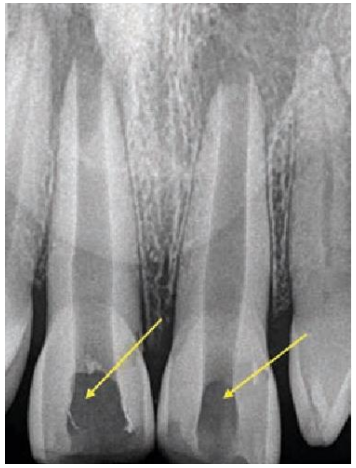
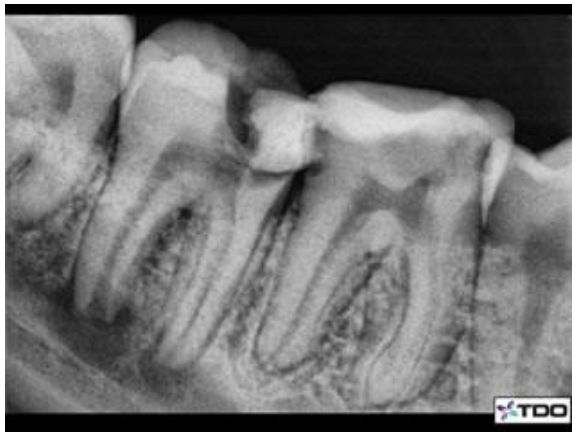

Dr. Saurabh Doshi
Style Italiano Endodontics



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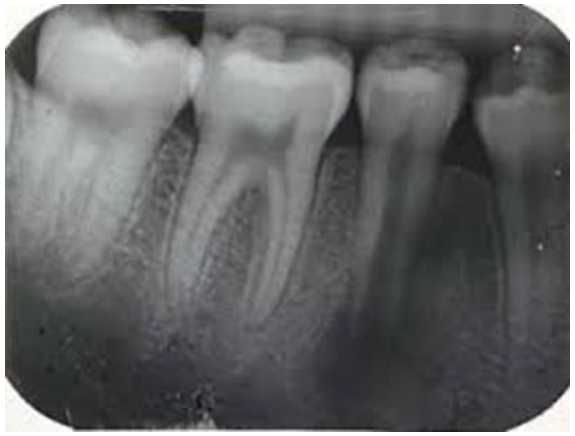
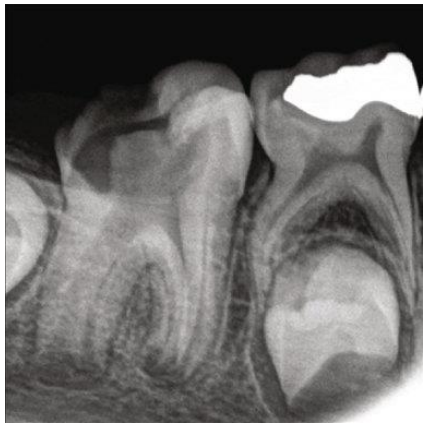
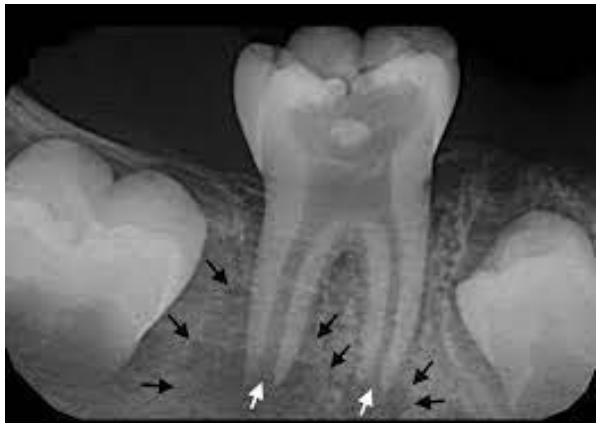






Endodontic management of immature tooth

- Conventional endodontic treatment of permanent teeth with incomplete root development is impossible, due to the significant risk of complications, including root fracture (the walls are thin and roots are short) or the accidental injection of fluids or filling material beyond the wide root apex

- The endodontic management of immature teeth
  - *Apexogenesis*: Keeping all or part of the pulp alive, allowing the root to develop naturally
  - *Apexification*: if the pulp is non-vital, stimulating the formation of hard tissue barrier in its apical part

Endodontic management of immature tooth

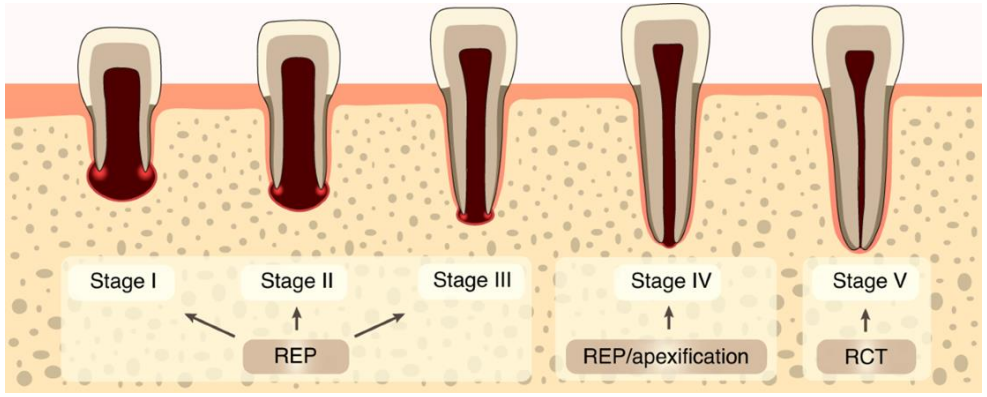
- The apexification has many disadvantages
- The calcium hydroxide is repeated placement, carries the risk of reinfection and thorough instrumentation inside the root canal may cause weakening of canal walls
- MTA or Biodentin, an alternative to calcium hydroxide, eliminates the problem of intracanal medication replacement
- However, none of these substances stimulates further root development

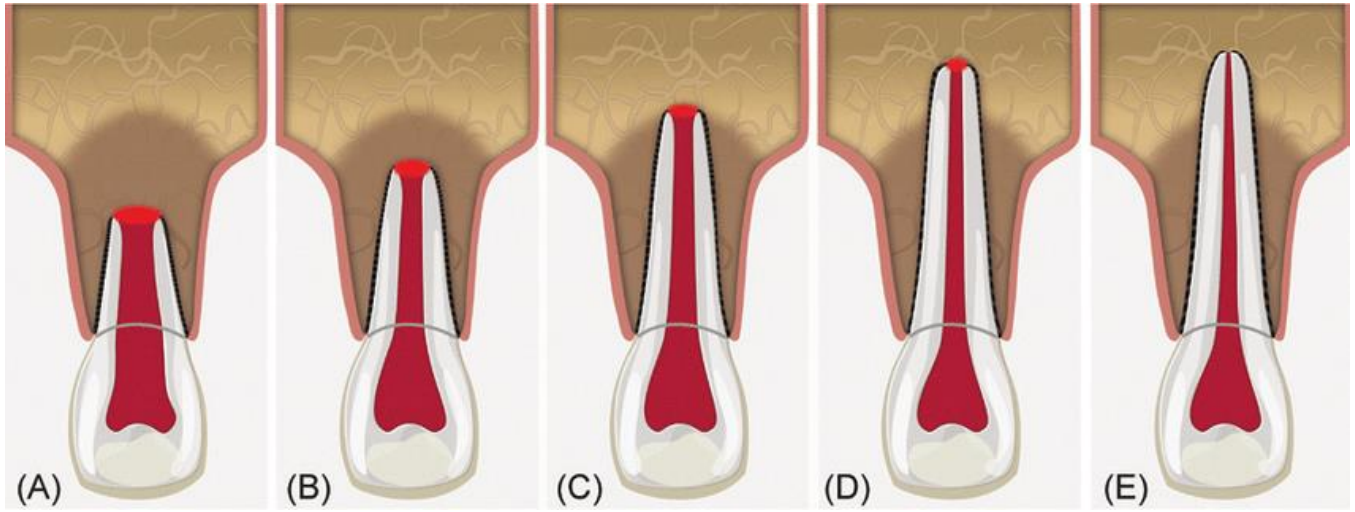
Endodontic management of immature tooth

- The regenerative endodontic procedure (REP), proposed in 2004 by Banchs and Trope
- Indications for REP include immature permanent teeth with necrotic pulp and inflammatory lesions of periapical tissue
- The main contraindications comprise significant destruction of the tooth tissues and a lack of patient cooperation
- The stage of root development and the width of apical opening, and the age and general health status of the patient influence therapy outcome

Endodontic management of immature tooth

- REP treatment is indicated primarily for teeth in stage 1-3 of root development, according to Cvek
- In almost-developed root with an open apex (stage 4), apexification treatment or REP should be considered
- REP is possible if the diameter of apical foramen is < 1 mm
- The highest success occurs in young patients between 9 and 18 years of age; the younger patient, the higher chances of successful therapy



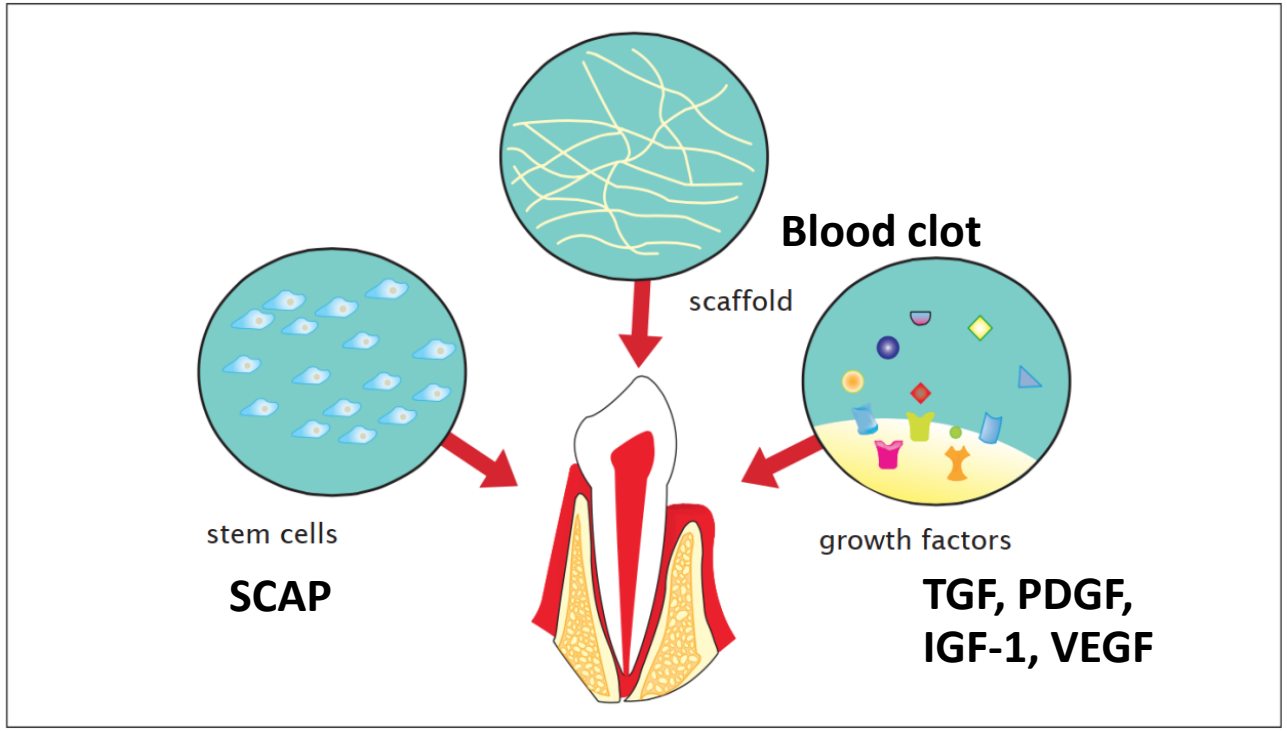


Endodontic management of immature tooth

- The key processes that occur in the root canal are angiogenesis, reinnervation and the differentiation of cells responsible for root development
- This leads to the formation of vital pulp, bone, cementum or periodontal like tissue in the canal and thus root formation
- The following stages of this procedure : disinfection of the canal, delivery of the REP components, closure of the cavity and follow-up appointments
- Three essential components must be present in the root canal : **a scaffold** for newly forming tissue, **stem cells** and **growth factors**

Tissue engineering

Tissue engineering is a fast-growing scientific field connecting the principles of medicine, engineering, and biology to **replace, restore, or regenerate tissues damaged or lost due to disease and/or trauma**



(Nomura et al., 2016)

European Society of Endodontology

European Society of Endodontology 2016

VS

American Association of Endodontists 2021

american association of endodontists

Procedural details (First appointment)

ESE: Revitalization 2016

- Tooth cleaning, local anaesthesia, field isolation and disinfection, access cavity
- Remove loose or necrotic pulp tissue and avoid mechanical instrumentation
- Irrigate with 1.5–3% sodium hypochlorite (20 mL, 5 min), use of side-vented needle, place 2 mm above vital tissue.
- Irrigate with sterile physiological saline (5 mL) to minimize the cytotoxic effects of sodium hypochlorite on vital tissues
- Dry with paper points
- Irrigate with 20 mL of 17% EDTA

AAE Revised 2021

- Local anesthesia, dental dam isolation and access.
- Lower concentrations of NaOCl are advised 1.5%-3% NaOCl (20mL/canal, 5 min) with irrigating needle positioned about 1 mm from root end, (e.g., needle with closed end and side-vents) to minimize cytotoxicity to stem cells in the apical tissues.
- Then irrigated with saline or EDTA (20 mL/canal, 5 min),

Procedural details (First appointment)

ESE: Revitalization 2016

- Insert calcium hydroxide into the root canal.
- The antibiotics, mainly triple antibiotic paste consisting of ciprofloxacin, metronidazole and minocycline were used with good results. Drawbacks such as discoloration, cytotoxicity, sensitization, development of resistance and difficulty of removal from the root canal.
- Place coronal seal directly onto intracanal dressing with a minimum thickness according to the material selected

AAE Revised 2021

- Place calcium hydroxide or low concentration of triple antibiotic paste.
- Seal with 3-4 mm of a temporary restorative material such as Cavit™, IRM™, glass ionomer or another temporary material. Dismiss patient for 1-4 weeks.

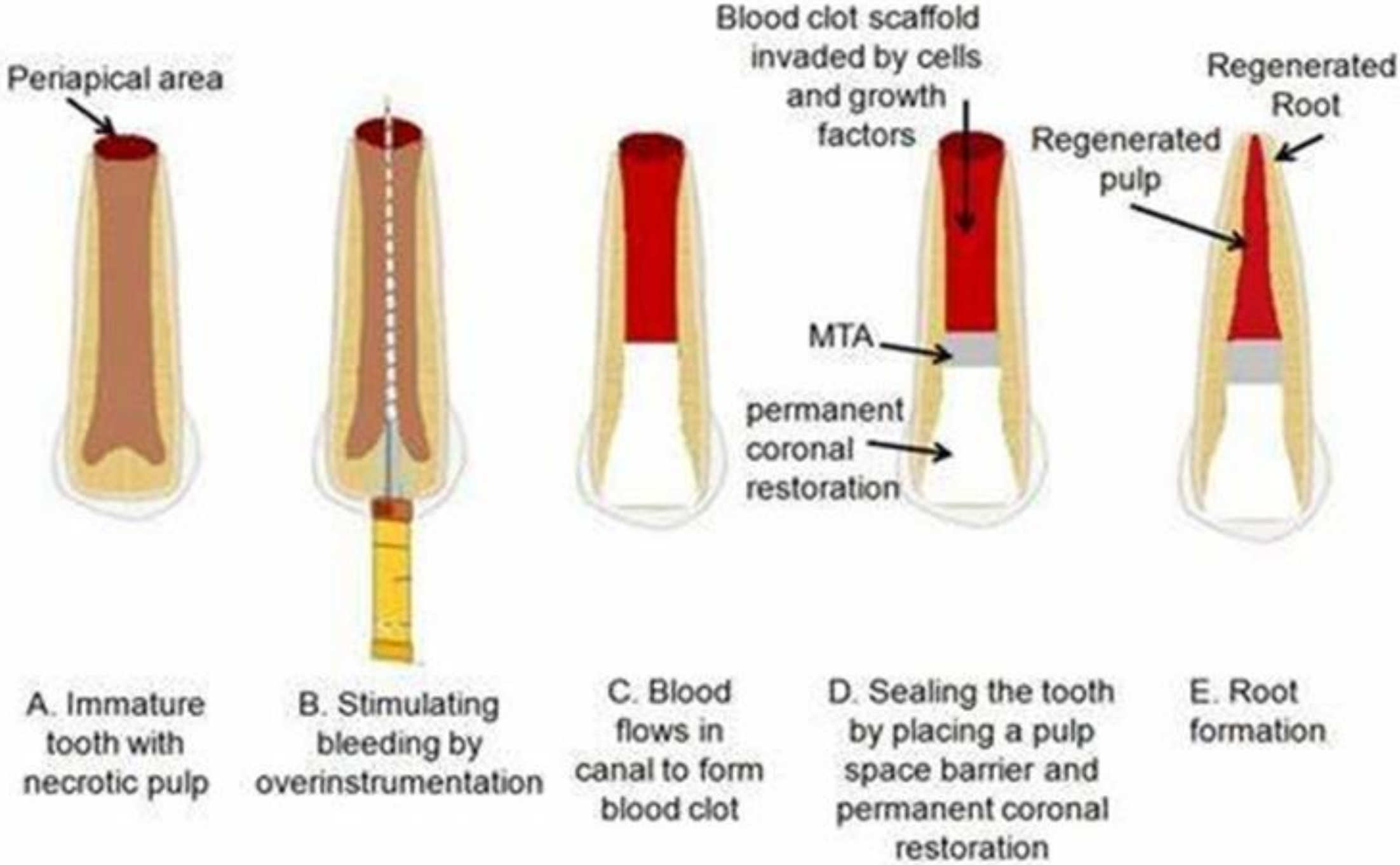
Procedural details (Second appointment)

ESE: Revitalization 2016 (2–4 weeks later)

- If signs of inflammation have not subsided, refresh calcium hydroxide.
- Cleaning, anaesthesia (Recommendations specify the use of anaesthetics without vasoconstrictor), field isolation and disinfection of operating field.
- Irrigate with 17% EDTA (20 mL, 5 min), use of side-vented needle and place 2 mm above vital tissue
- Irrigate with sterile physiological saline (5 mL) to reduce adverse effects of irrigants on target cells;
- Remove excess liquid with paper points;

AAE Revised 2021 (1–4 weeks later)

- If there are signs/symptoms of persistent infection, consider additional treatment time with antimicrobial, or alternative antimicrobial.
- Anesthesia with 3% mepivacaine without vasoconstrictor, dental dam isolation.
- Copious, gentle irrigation with 20 ml of 17% EDTA.
- Dry with paper points.


Periapical area
Blood clot scaffold invaded by cells and growth factors
Regenerated Root
Regenerated pulp
MTA
permanent coronal restoration
A. Immature tooth with necrotic pulp
B. Stimulating bleeding by overinstrumentation
C. Blood flows in canal to form blood clot
D. Sealing the tooth by placing a pulp space barrier and permanent coronal restoration
E. Root formation

Procedural details (Second appointment)

ESE: Revitalization 2016 (2–4 weeks later)

- Induce bleeding by mechanical irritation of periapical tissue and rotational movement of an apically pre-bent file (e.g. size 40 Hedstrom)
- canal to fill with blood until 2 mm below the gingival margin to wait for blood clot formation for 15 min

AAE Revised 2021 (1–4 weeks later)

- 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).
- Stop bleeding at a level that allows for 3-4 mm of restorative material.

Procedural details (Second appointment)

ESE: Revitalization 2016 (2–4 weeks later)

- Cut a collagen matrix, Collaplug or Hemocollagene to a diameter larger than the coronal part of the root canal and a height of 2–3 mm, place on top of the blood clot, allow the matrix to soak with liquid to avoid formation of a hollow space;
- Place a hydraulic silicate cement (e.g. MTA or tricalcium silicate cement) on top of the collagen matrix about 2 mm underneath the cement–enamel junction and beware of potential discoloration after contact of the material with blood;
- Apply a flowable, light-curable glass–ionomer or calcium hydroxide cement; Refresh the cavity walls with a diamond bur or grit blast with aluminium oxide, Seal with adhesive restoration.

AAE Revised 2021 (1–4 weeks later)

- Place a resorbable matrix such as CollaPlug™, Collacote™, CollaTape™ over the blood clot if necessary and white MTA as capping material.
- MTA has been associated with discoloration. Alternatives to MTA (such as bioceramics or tricalcium silicate cements) should be considered in teeth where there is an esthetic concern.
  - Anterior and Premolar teeth - Consider use of Collatape/Collaplug and restoring with 3 mm 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.
- A 3–4 mm layer of glass ionomer is flowed gently over the capping material and light-cured for 40 s.

Follow-up

ESE: Revitalization 2016

- Follow-ups should be performed after 6, 12 and 18 and 24 months, after that annually for 5 years
- A 3- month follow-up is recommended in cases of longstanding infection, difficult elimination of signs of inflammation, the presence of inflammatory root resorption or where alternative treatment has to be considered.
- bony healing should be awaited, and teeth after revitalization should be excluded from orthodontic treatment or follow-up intervals should be shortened during orthodontic treatment.

AAE Revised 2021

- 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

Follow-up (Success criteria)

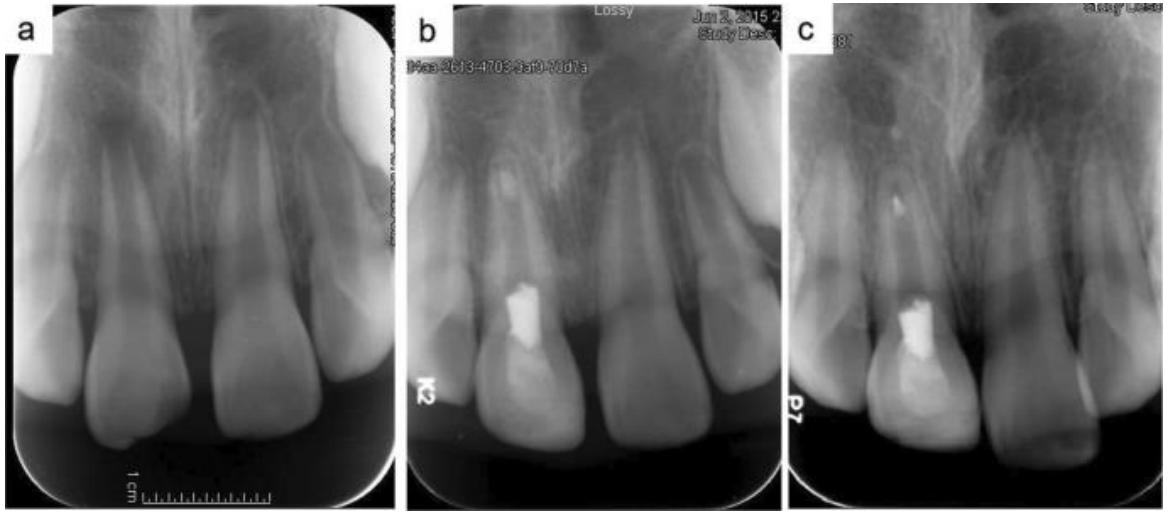
ESE: Revitalization 2016

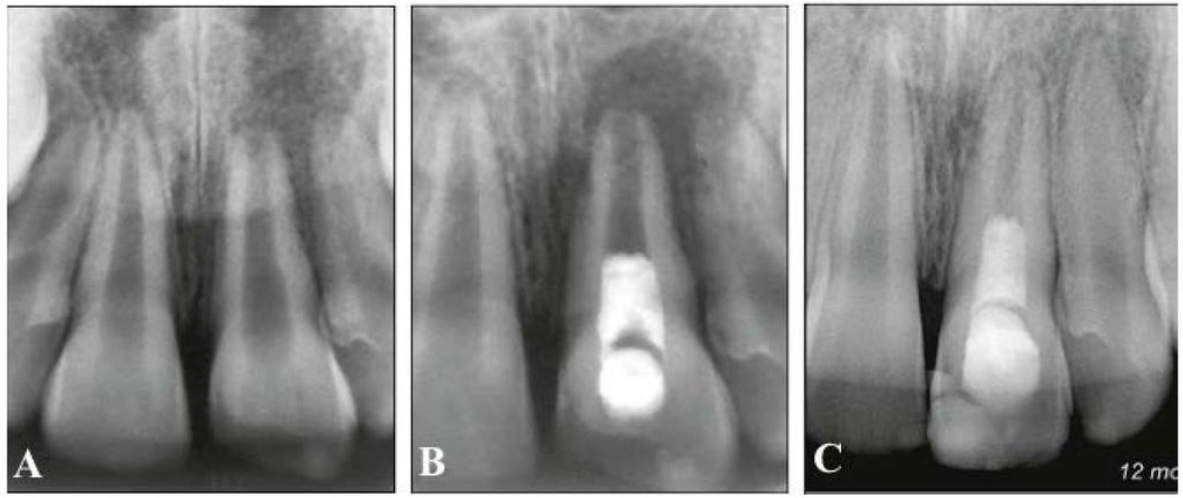
- No pain
- No signs and symptoms of inflammation
- Healing of pre-existing bony periapical lesion
- Increase of root thickness and length
- Absence of (continued) external root resorption
- Positive response to sensibility testing
- Patient acceptance
- No unacceptable color changes
- Radiographic detection of a new PDL along the inner wall of the root canal

AAE Revised 2021

- 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)

Review case REP





Tissue engineering

I. Stem cells

- Stem cells are defined as **highly proliferative, unspecialized cells,** which have the **ability to differentiation** into various other types of cells

- **Postnatal stem cells** have been identified in different body tissues, such as **bone marrow, peripheral blood, hair follicles, skin, intestine, adipose tissue, pancreas, and dental tissues**

- Studies indicate that dental pulp contains five types of mesenchymal stem cells (MSCs), which are noteworthy because of their pluripotent properties and easy method of isolation from exfoliated deciduous teeth

- It has been suggested, that dental pulp stem cells have the ability to differ not only into teeth tissues, but that they also have a neuronal and muscular differentiation capacity, and thus may play a key role in the future medical treatment of various diseases

Tissue engineering

I. Stem cells

1. Dental pulp stem cells (DPSCs)

- Clonogenic cells with high proliferation potential and long-term self-renewal, isolated from permanent third molars in 2000 by Gronthos et al.

- They reside within **niches in pulp chambers** in a stable microenvironment which depends on the interplay between growth factors, extracellular matrix proteins, receptor molecules, and stem cells

- Research has indicated that dental pulp stem cells have the ability to become **odontoblast-like cells and generate ectopic dentin** in the subcutaneous tissues of immunocompromised mice. Furthermore, it was shown that DPSCs can differentiate into other non-dental cells, such as **osteoblasts, odontoblast, chondrocytes** (thus, they can produce bone and cartilage tissues), **neuron cells, adipocyte, cardiomyocytes, and insulin-secreting Beta cells.**

Tissue engineering

I. Stem cells

2. Stem cells from exfoliated deciduous teeth (SHED)

- Isolated by Miura et al., exhibiting multipotential differentiation properties and increased cell-population doublings in comparison to DPSCs

- It is hypothesized that SHED cells have an extensive proliferation ability higher than DPSCs and MSCs derived from bone marrow, due to being a more proliferation

Tissue engineering

I. Stem cells

3. Stem cells from apical papillae (SCAP)

- MSC-like cells located in the tooth root apex, discovered for the first time by Sonoyama et al. in the apical papilla of human immature permanent teeth. Studies performed in immunocompromised rodents showed the odontogenic potential of SCAP cells when multipotent stem cells were transplanted with hydroxyapatite/tricalcium phosphate particles.

- The regeneration of pulp-like tissue and dentin structure were observed. According to the conducted scientific studies, it is believed that **SCAP cells are involved in the formation of root dentin**, as a source of primary odontoblast , opposed **to DPSCs, which take part in reparative dentin formation, providing replacement odontoblast**.

Tissue engineering

I. Stem cells

4. Periodontal ligament stem cells (PDLSCs)

- These multipotent cells have the potential to develop into **cementoblast-like cells**, adipocytes, and chondrogenic cells. In vivo experiments have exhibited PDLSC's capacity to form cementum/PDL-like structures

5. Dental follicle precursor cells (DFPCs)

- Localized in a dental sac, also known as a dental follicle, a loose connective tissue that surrounds developing teeth, and also impacted teeth. The latter are usually extracted and disposed of, therefore there are no controversial ethical issues linked to the sourcing of DFPCs
- Some studies have shown that DFPCs can transform into fibroblasts, osteoblasts, periodontal ligament, and cementoblasts, thus these cells may be useful in regeneration therapies of periodontal tissues

Table 1. Stem cells involved in apexogenesis and REP.

Type	Function
Human Dental Pulp Derived Stem Cells (HDPSCs)	Differentiation toward odontoblasts, osteoblasts, adipocytes, neurons, initiation of angiogenesis
Stem Cells from Human Exfoliated Deciduous Teeth (SHEDs)	Differentiation toward odontoblasts, osteoblasts, adipocytes, neurons
Periodontal Ligament Stem Cells (PDLSCs)	Osteogenesis
Dental Follicle Stem Cells (DFSCs)	Differentiation toward odontoblasts, fibroblasts, osteoblasts, cementoblasts
Human Umbilical Vein Endothelial Cells (HUVECs)	Angiogenesis
Stem Cells from the Apical Papilla (SCAPs)	Differentiation toward odontoblasts

Tissue engineering

II. Growth factors

- **Growth factors** are extracellular proteins or polypeptides, which interact with specific-cell receptors to **activate intracellular signaling cascades**, eventuating in cell proliferation, differentiation, migration, and the apoptosis of numerous different cell types, including dental pulp cells and stem cells

- Growth factors differ in their functions, thus they may be used in many biomedical applications

- Stimulation of **cellular division and differentiation** are coordinated by several growth factors, such as fibroblast growth factors **(FGF),** platelet-derived growth factor **(PDGF),** epidermal growth factor **(EGF),** and insulin-like factor **(IGF)**. Others are known as wound-healing promoting factors, as in the case of **TGF-β** superfamily-types 1, 2, and 3

Tissue engineering

II. Growth factors

- Scientific research has revealed that growth factors like **PDGF, TGF, IGF-1, EGF, and FGF** may participate in dentin regeneration processes when damage occurs, furthermore, the important role of these signaling molecules in stem cell maintenance and their contribution to dental tissues regeneration was considered

- Moreover, two distinct families of growth factors, crucial for tooth formation and regeneration, are **vascular endothelial growth factor (VEGF)** and **bone morphogenetic protein (BMP)**

Tissue engineering

II. Growth factors

- **VEGF**, also known as vascular permeability factor (VPF), is a **major angiogenic factor**, with a specific affinity to endothelial cells (ECs)
- The function of VEGF **activates blood vessel formation and homeostasis** by stimulating migration, proliferation, and increased survival of endothelial cells in the hypoxic environment
- It is well accepted that the vascular network, in providing oxygen and nutrients, is essential for tissue development and repair, and thus VEGF may be a **beneficial element for pulp regeneration**

Tissue engineering

ll. Growth factors

- **BMPs** belong to the transforming growth factor-β (TGF-β) superfamily of proteins, and are responsible for diverse biological functions

- They act as potent regulators of **proliferation, migration, and differentiation of MSCs into osteoblasts and chondroblasts**, and thus they play a pivotal role in skeletal development

- In addition, in vivo and in vitro studies have shown the requirement of BMP activity in the early stages of odontogenesis, due to its ability to induce the transformation of **pulp stem cells into odontoblasts**

- Based on past findings, it has been suggested that **BMPs may be a key element for dental tissue regeneration**, especially recombinant human **BMP-2**, by virtue of its capability to convert adult pulp progenitor cells into odontoblast-like cells

Table 2. Growth factors involved in apexogenesis and REP.

Type	Function
Bone Morphogenetic Protein (BMP)	Dentinogenesis
Vascular Endothelial Growth Factor (VEGF)	Proliferation, angiogenesis
IGF Insulin-like Growth Factor (IGF)	Proliferation
TGF-β Transforming Growth Factor-β (TGF-β)	Migration, proliferation
FGF Fibroblast Growth Factor (FGF)	Migration, proliferation, dentinogenesis
Platelet-Derived Growth Factor (PDGF)	Migration, angiogenesis

Tissue engineering

III. Scaffold

- As a third component in the tissue engineering triad, the scaffold is described as a **three-dimensional (3D)** biocompatible material that provides mechanical support for bioactive molecules or cells, and acts as an extracellular matrix template, predisposing the adhesion and proliferation of a specific cell type, such as pulpal cells

- Ideally, the scaffold should have **high porosity to facilitate cells deposition**, and **to permit effective nutrient and gas exchange**

- Moreover, it should have the proper physical and mechanical properties, and also be entirely biodegradable

- However, the scaffold degradation must be equal to a formation rate of new tissue

Tissue engineering

III. Scaffold

- There are various types of scaffolds known, based on their origin; **natural scaffolds** (e.g., collagen, hyaluronic acid, Platelet-rich fibrin (PRF), Platelet-rich plasma (PRP), blood clot, chitosan) and **artificial scaffolds** (e.g., polymers of polyglycolic acid, polylactic acid, polyepsilon caprolactone, glass–ceramic, and bioactive glasses) differ in attributes and properties

- Scaffold technology has shown promising advancements in regenerative dentistry, scientifically demonstrated in immunodeficient mice

- The researchers obtained a regeneration of dentin-like tissue in disinfected and emptied root canal using a porous polymer scaffold seeded with stem cells, after transplantation into an animal model

Table 3. Selected substances proposed as scaffolds in regenerative endodontics.

Scaffold	Origin	Chemical Structure	Characteristics
Fibrin	Natural	Protein	Low-cost, biocompatible, derived from blood plasma, does not induce an immune response
Silk	Natural	Protein	Biodegradable, biocompatible, does not induce an immune response
Chitosan	Natural	Polysaccharide	Biocompatible, biodegradable, may cause allergic reactions
Hyaluronic acid	Natural	Polysaccharide	Biocompatible, low immunogenic potential, hydrogel-forming extracellular matrix
Collagen	Natural/ synthetic	Protein	Biocompatible, low immunogenic potential, hydrogel-forming extracellular matrix
Self-assembling peptides	Synthetic	Peptides	Biocompatible, forming hydrogels
Polylactic acid (PLA), Polyglycolic acid (PGA), Poly(lactide-co-glycolide) (PLGA)	Synthetic	Polyesters	Biocompatible, biodegradable, may cause slight inflammatory reactions
Bioactive ceramics	Synthetic	Calcium phosphates, Bioactive glasses (mixture of sodium silicon oxides, calcium, magnesium, iron, etc.)	Biocompatible, low immunogenic potential, osteoinductivity

Tissue engineering

III. Scaffold

- After periapical tissues laceration with a hand file to induce bleeding into the canal space, the flowing blood may bring mesenchymal stem cells, immunoglobulins, cytokines, and growth factors

- Another purpose is blood clot formation, which may act as a scaffold

- Intracanal bleeding plays a key role in pulp–dentin complex repair

- The simplest way to obtain a scaffold in the root canal is to induce bleeding from the periapical region, which causes blood to flow into the canal and form a clot

- However, blood clot contains few growth factors

Tissue engineering

III. Scaffold

- PRP, the platelet concentration obtained from patient plasma, acts as both scaffold and a rich reservoir of cytokines and growth factors released from platelet α granules
- PRF is a newer substance, a so-called second generation platelet concentrate, containing a fibrin membrane enriched in platelets, growth factors and cytokines
- Limitations of the PRF or PRP method are the need for venous blood sampling, the need for specialized equipment and difficulty in applying the substance to the canal due to gelatinous consistency
- Shivashankar et al. found comparably high efficacy of PRP, PRF and blood clot in stimulating root growth, while PRP was best for healing the periapical region

Disinfection the canal

- An infected immature permanent tooth with an open apex exhibits greater potential to achieve a positive result of endodontic treatment than mature teeth, due to rich vascularization

- One of the major problems of necrotic immature teeth is controlling the infection by obtaining a complete eradication of bacterial biofilm in the complex root canal system

- Leaving microorganisms on the canal walls or in the dentinal tubules prevents the development of new tissue and creates a risk of periapical tissue inflammation

Disinfection the canal

Irrigation: **NaOCl**

- NaOCl in a concentration ranging from 1% to 5.25% is effective against biofilm formed by highly resistant *Enterococcus faecalis*

- The higher concentrations of sodium hypochlorite have a toxic effect on the survival of stem cells from the apical papilla (SCAP)

- The current regenerative endodontics guidelines recommend using 1.5%–3% NaOCl

- This concentration of the irrigant exhibited minimal harmfulness for SCAP and odontoblasts

- Heating 2.5% NaOCl to 37°C results in its disinfecting potential reaching the same level as the 5.25% NaOCl solution

Disinfection the canal

Irrigation: **EDTA**

- EDTA has the ability for smear layer removal from instrumented root canal walls

- In addition, the chelating effect after EDTA promotes the release of growth factors from dentinal tubules, migration and differentiation of stem cells, and adhesion of newly forming tissue to the root canal walls

- The noxious effect of NaOCl could be reversed by the usage of 17% EDTA after NaOCl irrigation

Disinfection the canal

Instrumentation

- Complete instrumentation may be unfavorable for regenerative treatment, by removing vital tissues from the apical area of the canal and also weakening root walls

- Nevertheless, mechanical debridement seems to be required for biofilm structure removal, because its remaining causes persistent inflammation, and significantly decreases the chance of regenerative procedure success

- The apical foramen width seemed to affect the outcomes of REP in teeth with necrotic pulp, nevertheless, the minimum diameter has not been determined

- Recent studies demonstrated that the most successful treatment was conducted with a foramen width of 0.5–1.0 mm

Disinfection the canal

Intracanal medicament: **Antibiotic paste**

- The antibiotic medicament, commonly known as a triple antibiotic paste (TAP), contains a combination of ciprofloxacin, minocycline, and metronidazole

- The combination of drugs guarantees effective antibiotic activity against microorganisms present in the root canal

- Minocycline is proven to be non-cytotoxic, inhibit collagenase and metalloproteinases and increase the anti-inflammatory cytokine IL-10, whereas metronidazole and ciprofloxacin can stimulate fibroblast formation

- Antibiotic usage is always associated with the risk of systemic allergic reaction

Disinfection the canal

Intracanal medicament: **Antibiotic paste**

- The several disadvantages were also reported, such as cytotoxicity against stem cells, risk of tooth discoloration, development of drug resistance and difficult removal from the canal

- Tooth structure discoloration is one of the side effects caused by the minocycline included in triple antibiotic paste

- To reduce the risk of minocycline-induced crown discoloration, the paste should be applied into canal does not above the CEJ. Some authors suggest the use of self-etching bond system to seal the dentinal tubule

- The alternate use of amoxicillin or cefaclor or a dual-antibiotic paste (DAP)

- Both TAP and DAP decrease the survival of stem cells of the apical papilla (SCAP) when used in a concentration greater than 1000 mg/mL as a canal dressing

Disinfection the canal

Intracanal medicament: **Calcium hydroxide**

- Calcium hydroxide is also much easier to rinse it out completely from the root canal compared to TAP

- After irrigation, up to 80% of TAP may remain in the root canal and still negatively affect stem cell survival

- Calcium hydroxide showed improvement of SCAP proliferation and no cytotoxic properties

- Usage of calcium hydroxide as a canal dressing for a long period of time may lead to weakening root dentine and increasing the possibility of root wall fracture

- The latest study on root susceptibility to fracture after long-term calcium hydroxide treatment, revealed that root fracture might be more associated with root stage development than the use of the examined material

Disinfection the canal

Intracanal medicament

- **Propolis** can be comparable with TAP as a disinfection treatment option in regenerative endodontic

- After irrigation, up to 80% of TAP may remain in the root canal and still negatively affect stem cell survival

- The **photoactivated disinfection (PAD)** was successfully used in root canal disinfection of mature teeth and attempted to use it in REP

- It is based on activating a photosensitizer with low-power laser light at an appropriate wavelength

- The energy causes the formation of a reactive oxygen species (ROS), which is responsible for destruction of bacterial cells

Scaffold capping material

- A mineral trioxide aggregate (MTA) cement is placed over the blood clot or scaffold to seal the root canal space, and prevent bacterial invasion

- MTA is considered to have a potential for discoloration of coronal dentine

- Another disadvantage of MTA is its long setting time (2h and 45 min), which increase its porosity as a sequence increases blood absorption

- Alternatives to MTA, such as Biodentine can be used to avoid the risk of this negative outcome

- The Biodentin is lack of bismuth oxide in its composition, much shorter setting time (12 min) and a lower rate of tooth discoloration

- Recent research revealed a higher shear bond strength value between calcium silicate-based cement (such as Biodentine and MTA) overlaid with resin-based composite than glass ionomer

Follow-up

- There are no standardized recall protocols

- A complete follow-up should include a radiographic and clinical examination

- The periapical radiographs allow verifying the increase of root length and width of root walls, and also the resolution of an apical radiolucency

- The clinical examination should record a positive response to the pulp vitality test, no pain for percussion/palpation, and normal soft tissue appearance

- Practicable time-intervals for follow-ups are at 3, 6, 12, 18, and 24 months

Conclusions

- Pulp revascularization procedure may bring a favorable outcome, however, the prognosis of REP is unpredictable

- Infected immature permanent teeth may have a greater potential to achieve a positive result with endodontic treatment than mature teeth

- Mature teeth also revealed healing processes and became asymptomatic

- A common goal of eliminating periapical tissue inflammation and restoring the pulp–dentin complex

- Generally, the treatment protocol for regenerative endodontics included minimal or no mechanical instrumentation, canal irrigation with NaOCl, triple antibiotic paste (TAP) as an intracanal medication, and MTA as capping material

Conclusions

- The REP may become the standard for treating immature permanent teeth with necrotic pulp in the near future

- The formation of living tissue in the root canal with stem cells, growth factors and scaffolds is a milestone on endodontics

- In addition, it is necessary to develop an optimal management protocol in specific cases

- The need for comparative analysis of the long term effectiveness of REP and apexification is also indicated

Conclusion

- Based on moderate-quality evidence, REPs appear as a viable treatment alternative for mature necrotic teeth with periapical lesions at present
- Longstanding debates in the endodontic community on the limitations of apical preparation, apical size and its control, obturation materials, the effect of heating, and more might have no place in this relatively new treatment procedure.

Thank you