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Management Strategies for Immature Teeth with Pulp Necrosis: An Umbrella Review of Systematic Reviews

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Introduction: This review evaluates the effectiveness of treatment modalities for immature teeth with pulp necrosis, focusing on calcium hydroxide (CH) and mineral trioxide aggregate (MTA) apexification, as well as regenerative endodontic treatments (RETs). Recent advancements and clinical outcomes are highlighted. **Materials and Methods**: A comprehensive search of MEDLINE (PubMed), Embase, Cochrane Library, Scopus, and grey literature was conducted from inception to July 2024. Systematic reviews and meta-analyses (SR/MAs) assessing apexification and RET outcomes in immature teeth with pulp necrosis were included. Studies were selected based on predefined criteria, and data on study design, interventions, and outcomes were extracted. Methodological quality was evaluated using the AMSTAR-2 tool. **Results**: 31 SR/MAs were included. The quality ranged from critically low to low, except one rated as high. MTA apexification was more effective than CH for faster apical barrier formation, though overall success rates were similar. MTA is preferred for its efficiency, but standardized protocols are needed, and tooth discoloration was noted as a potential complication. RET generally outperforms apexification in root maturation, with platelet concentrates like platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) showing promising results; PRP was associated with greater root length, while PRF showed superior apical healing. Variability in RET outcomes was noted due to the lack of standardized protocols. Comparative studies of RET versus apexification showed no significant differences in survival or overall success rates. RET often provides better apical closure and root development, though results vary. Both approaches are viable, but more research with standardized protocols and larger samples is needed to establish definitive clinical advantages. **Conclusions**: MTA apexification and RET are viable alternatives to CH apexification, with RET showing greater potential for root development and apical healing. Future research should focus on developing standardized protocols and uniform RET guidelines, and evaluating long-term outcomes to establish efficacy and safety.

Keywords: Apexification; Calcium Hydroxide; Endodontics; Immature Permanent Teeth; Mineral Trioxide Aggregate; Necrotic Teeth; Pulpotomy; Regenerative Endodontics; Root Development; Systematic Review

Introduction

Managing immature permanent teeth with pulp necrosis remains a significant challenge in endodontics and pediatric dentistry due to the complexities associated with incomplete root development [1]. Traditional treatment approaches, such as apexification, have been employed to manage these challenges by facilitating root canal therapy and inducing apical closure.

Calcium Hydroxide (CH) Apexification

CH apexification has been a longstanding method for managing immature teeth with pulp necrosis [2]. This technique involves placing CH within the root canal to stimulate the formation of a calcified barrier at the root apex. While effective in disinfecting the root canal system and inducing apical closure, CH apexification typically requires extended treatment periods, ranging from 9 to 24 months [3]. The extended use of intracanal application of CH can weaken the tooth structure, increasing the risk of cervical root fractures and potentially compromising the long-term prognosis of the treated tooth.

Mineral Trioxide Aggregate (MTA) Apexification

In response to the limitations of CH apexification, MTA, a calcium silicate-based cement (CSC), emerged as a promising alternative [4]. The MTA-apical plug technique involves placing MTA or other calcium silicate-based cements (CSCs) at the root apex to create an artificial barrier and facilitate root canal obturation [5-7]. CSCs offer several advantages over CH, including shorter treatment time and better biocompatibility, which facilitates favorable interactions with periapical tissues and supports healing. Despite these benefits, MTA and other CSCs do not notably enhance root formation or dentin wall thickening, and tooth discoloration remains a drawback [8].

Regenerative Endodontic Treatments (RET)

RET represents a paradigm shift in the management of immature teeth with pulp necrosis [9]. Unlike apexification strategies that focus on forming a calcified barrier, RET aims to regenerate the pulp-dentin complex [10]. This biologically based approach usually results in continued root development and thickening of dentin walls by revitalizing the tooth [11-13]. RETs, often utilizing platelet concentrates (PCs) such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), have shown promising results in root maturation [14]. However, inconsistent outcomes and a lack of standardized protocols emphasize the need for further research to refine treatment strategies and achieve consistent success.

Objectives of the Review

This review aims to critically assess and compare the effectiveness of different management strategies for immature teeth with pulp necrosis, specifically focusing on CH apexification, MTA apexification, and RETs. By synthesizing evidence from systematic reviews and meta-analyses (SR/MAs), this umbrella review seeks to:

1) Evaluate the efficacy of CH versus MTA apexification and RETs in treating immature teeth with pulp necrosis.
2) Highlight recent advancements and their impact on treatment outcomes.
3) Identify gaps in the current evidence base and suggest directions for future research

Materials and Methods

Protocol

This study was conducted based on a high-quality methodological review and the Cochrane Handbook [15].

Search Strategy and Databases

A comprehensive systematic search was conducted to identify relevant literature up to July 2024. The following databases were searched: MEDLINE (PubMed), Embase, Cochrane Library, Scopus. No language restrictions were applied to ensure a broad scope of relevant studies. The search utilized a combination of keywords and phrases, including "immature necrotic teeth," "apexification," "calcium hydroxide," "mineral trioxide aggregate," "regenerative endodontic treatments," and "clinical outcomes." Additionally, a manual search of reference lists from relevant articles was performed to capture any studies that may have been overlooked by the database searches. This approach aimed to ensure the inclusion of all relevant SR/MA related to the management of immature teeth with pulp necrosis.

Eligibility Criteria

This review included SR/MA evaluating outcomes related to apexification, and REPs for immature teeth with pulp necrosis. The eligibility criteria were as follows:

1) **Inclusion Criteria*:*** Included were SR/MA that assessed clinical outcomes of CH/MTA apexification techniques and RETs for immature teeth with pulp necrosis. Eligible studies were required to be published in peer-reviewed journals and provide comprehensive data on the clinical outcomes related to the management of immature teeth with pulp necrosis.
2) **Exclusion Criteria*:*** Studies were excluded if they did not specifically focus on immature teeth with pulp necrosis. Additionally, case reports, case series, observational/ experimental studies, opinion articles, and SR/MA that lacked sufficient data on clinical outcomes were not considered.

Study Selection and Data Extraction

Two reviewers (S.A. and S.S.) independently performed study selection and data extraction according to the predefined search strategy. After removing duplicate articles, the reviewers screened the titles and abstracts for relevance. Full-text articles were then examined to confirm eligibility. Any discrepancies between reviewers were resolved through discussion. The following information was systematically collected from the included studies:

1) **Study Design**: The study type (SR/MA)
2) **Interventions**: Detailed description of apexification and RET techniques, including specific protocols and materials used
3) **Outcomes:** Clinical/radiographic outcomes related to survival/success rates, periapical healing, apical barrier formation time, apical foramen width, apical closure, root development, dentinal wall thickness, pulp vitality, and any reported adverse effects or complications.

Quality Assessment

The methodological quality and risk of bias of included SR/MAs were evaluated using the AMSTAR-2 tool [16]. This evaluation assessed the clarity of research questions, the specificity of inclusion criteria, adherence to pre-established review protocols, the justification for any methodological deviations, and the rationale behind the selected study designs. It further evaluated the comprehensiveness of the literature search, the duplication of study selection and data extraction processes, the transparency in reporting excluded studies, and the adequacy of study descriptions. The assessment also considered the robustness of risk of bias assessment methods, the disclosure of potential conflicts of interest, the appropriateness of statistical methods used in meta-analyses, and the handling of heterogeneity and publication bias.

Based on the AMSTAR-2 suggested decision rules, each included review was given an overall confidence rating of 'critically low' (more than one critical flaw with or without non-critical weaknesses), 'low' (one critical flaw with or without non-critical weaknesses), 'moderate' (more than one non-critical weakness), or 'high' (no or one non-critical weakness) [16].

Limitations

This review acknowledges potential limitations, including variations in study designs, differences in outcome measures, and the quality of evidence across studies. The results should be interpreted with these limitations in mind.

Results

Search results

Initially, 1100 papers were retrieved from the mentioned databases. After screening the titles/abstracts and removing duplicates, 250 underwent full-text review based on the selection criteria. Finally, 31 SR/MAs were included in the final analysis.

Study characteristics

Tables 1-3 outline the characteristics and qualitative synthesis of the included studies. Out of the 31 studies, 12 were systematic reviews (SRs) and 19 were SR/MAs. The studies included randomized controlled trials (RCTs), clinical studies, observational studies, case series/reports. The publication years ranged from 2011 to 2024.

The included reviews evaluated various treatments for immature and mature teeth with necrotic pulp. Pulp necrosis was diagnosed and assessed through a combination of clinical examination and radiographic findings. The age range in some reviews varied from 6 to 58 years. The studies differed in design and measured outcomes, leading to heterogeneity in the dataset, which precluded the conduct of a meta-analysis.

Summary of evidence

i) Apexification with Different Materials

Five SR/MA (3 SR/MAs and 2 SRs) have evaluated the efficacy of different materials (*i.e.*, CH, MTA and other CSCs) for apexification in immature permanent teeth [17-21] (Table 1). The evaluated outcomes included success rates, apical closure, and the time required for apical barrier formation.

- Shaik *et al.*'s SR/MA compared MTA, CSCs, and CH for apexification. While all materials demonstrated comparable clinical outcomes, MTA and CSCs were found to induce apical barrier formation more rapidly than CH. The average time required for apical closure was significantly shorter with MTA and CSCs, suggesting their potential superiority for accelerated treatment [17].

Table 1. Summary of SR/MA Studies Comparing Different Materials for Apexification in Immature Teeth with Pulp Necrosis

Study (Year)	Design (n)	N (Age)	Materials Compared	Key Findings
Shaik *et al.* (2021) [17]	RCT/CT (9)	328 (6-18)	MTA *vs*. CH, CSC	***Clinical success rates*** no sig. difference between CH (n=66), MTA (n=155) and CSC (n=66); ***apical barrier formation time*** superior results of MTA (n=155) and CSC (n=65) than CH (n=65)
Nicoloso *et al.* (2017) [18]	RCT (4)	110 (6-18)	MTA *vs*. CH	***No MA***; ***overall success rates*** no sig difference between CH and MTA in one study; ***apical barrier formation*** After 12 months, sig greater results for MTA than CH in one study; ***apical barrier formation time*** in two studies superior results for MTA than CH
Lin *et al.* (2016) [19]	RCT (4)	80 (6-12)	MTA *vs*. CH	***Clinical success rates*** no sig difference between MTA *vs*. CH; ***radiographic success rates*** no sig difference between MTA *vs*. CH; ***apical barrier formation*** no sig difference between MTA *vs*. CH; ***apical barrier formation time*** superior results of MTA *vs*. than CH
Chala *et al.* (2011) [20]	RCT (2)	50 (6-15)	MTA *vs*. CH	***Clinical success rates*** no sig difference between MTA (n=25) and CH (n=25); ***apical barrier formation*** no sig difference between MTA (n=25) and CH (n=25)
Panda *et al.* (2022) [21]	RCT, NRCT (3)	118 (NS)	MTA *vs*. Collagen/ MTA, CH	***No MA***; ***periapical healing*** no sig difference between CH (n=34) *vs*. MTA (n=34) in one study. However, in 2 studies, MTA (n=15) and collagen sponge/MTA (n=10) lead to a greater result than CH (n=34) and MTA apical plug (n=10), respectively

RCT: *Randomized Controlled Trial;* ***NRCT:*** *Non randomized Controlled Trial;* ***NS:*** *Not stated;* ***CT:*** *Clinical Trial;* ***CSC:*** *Calcium ciliate-based cement;* ***MTA:*** *Mineral Trioxide Aggregate;* ***CH:*** *Calcium Hydroxide;* ***Sig:*** *significant.*

- Nicoloso *et al*. compared MTA to CH in a SR, and found it to exhibit superior apical barrier formation; this study highlighted the advantages of MTA regarding both the clinical outcomes and radiographic evidence of apical barrier formation. However, in one study, CH and MTA showed similar success rates [18].
- Lin *et al*. [19] and Chala *et al*. [20] compared MTA and CH for apexification and concluded that MTA achieved faster apical barrier formation with clinical success comparable to CH.
- Panda *et al*. compared MTA to MTA/collagen and CH for apexification without performing meta-analysis and found inconsistent results regarding periapical healing; since one paper showed similar efficacy of MTA *vs*. CH, the other papers found the greater results of MTA over CH and MTA/collagen over MTA [21].

Three SR/MAs reported similar success rates for apexification with MTA compared to CH [17, 19, 20]. Two SR/MAs found comparable apical closure between MTA and CH [19, 20]. However, regarding apical barrier formation time, MTA had superior results [17, 19]. Overall, MTA demonstrated equivalent clinical outcomes to CH, with the added benefit of faster apical barrier formation, making it a preferred material for apexification. ***Bottom line:*** These studies consistently indicate that MTA is more effective than CH for apexification in immature teeth with pulp necrosis, particularly due to faster apical barrier formation. While overall clinical success rates between MTA and CH are often similar, MTA generally shows quicker apical barrier formation and, in some cases, better outcomes. This trend is significant in several studies but not universally observed. The findings suggest MTA may be the preferred choice for its efficiency in apical barrier formation. However, the variability in results highlights the need for standardized protocols and consistent outcome measures to better compare materials and establish clear clinical guidelines.

ii) RET with different scaffolds

A total of 19 studies (8 SRs and 11 SR/MAs) explored various scaffolds (i.e., blood cloth [BC], PCs, autologous PCs (APCs), platelet pellet [PP], combinations of BC with collagen, collagen/Placentrex, fibroblast growth factor-2 [FGF-2], poly lactic-co-glycolic acid [PLGA], chitosan, PC/collagen, and mesenchymal stem cell transplantation) in RETs [21-39] (Table 2). The evaluated clinical/radiographic outcomes included survival/success rates, pulp vitality, periapical healing, apical closure, dentinal wall thickness, and root length.

- Kiaipour *et al.* [22] and Pryia *et al.* [23] compared the regenerative potential of BCs to PCs in SRs and found contraindicating results. Kiaipour *et al,* reported that some studies showed greater periapical healing, root length, apical closure, and dentinal wall thickness with PCs, while others found similar effects between PCs and BCs [22]. Pryia *et al.* observed comparable vitality responses in one study, but results regarding success rates and periapical healing were inconsistent; some studies favored PCs, while others did not. These findings suggest that PCs may have superior regenerative capabilities compared to BCs; however, no meta-analysis was performed [23].
- Panda *et al.* compared APCs to BCs and found that APCs resulted in greater, apical closure and vitality response, with comparable success rates. However, APCs and BCs showed similar outcomes regarding root length and dentinal wall thickness, indicating that PCs might have superior regenerative capabilities compared to BCs [24].
- Yang *et al.* [25], and Tang *et al.* [27] also found that PCs were comparable to BCs and other scaffolds in promoting pulp vitality, root development and apical closure. Sabeti *et al.* specifically emphasized the effectiveness of PRP, PRF, PP, BC/collagen and BC/FGF-2 over BC, showing greater results in promoting periapical healing and root development [26].
- Vatankhah *et al.* reported high clinical success rates with RET using BC, PRP, or PRF; however, BCs resulted in higher vitality rates. While PRF showed the highest periapical healing rate, the differences were not significant [28].
- Li *et al.* found high success rates with no significant difference between immature and mature teeth treated with RETs [29]. Shaik *et al.* reported high success rates in RETs for immature teeth, with significant apical closure and increases in root length [30].
- Ríos-Osorio *et al.* [31] and Pecci-Lloret *et al.* [32] compared various scaffolds without performing meta-analyses. Ríos-Osorio *et al.* found inconsistent results regarding whether PRP and PRF were superior to BC in terms of root length, dentinal wall thickness, apical closure, and periapical healing outcomes [31]. However, Pecci-Lloret *et al.* emphasized the need for more RCTs to establish definitive conclusions [32].
- Kharchi *et al.* investigated the use of non-antibiotic disinfection in RET and analyzed outcomes such as clinical sign/symptoms (i.e., pain, sinus involvement, and swelling), pulp vitality, apical closure, root length, and dentinal wall thickness and found satisfactory results; however, no meta-analysis was conducted [33].
- Ong *et al.* [34] conducted a comprehensive SR/MA, showing high survival and healing rates of 97.3% and 93.0%, respectively. However, root development was found to be unpredictable.

Table 2. Summary of SR/MA Studies on Regenerative Endodontic Therapy (RET)

Author (Year)	Design (n)	N (Age)	Root Status	Scaffolds	Key Findings
Panda *et al.* (2022) [21]	RCT/ NRCT (8)	200 (NS)	Immature	BC *vs.* PC	***Pulp vitality*** greater results of PC (n=44) than BC (n=40); ***overall success rates*** no sig difference between BC (n=51) *vs.* PC (n=55); ***apical foramen width*** no sig difference between BC (n=112) *vs.* PC (n=121); ***dentinal wall thickness/root length*** no sig difference between BC (n=54) *vs.* PC (n=63)
Kiaipour *et al.* (2023) [22]	RCT (13)	392 (7-20)	Immature	BC *vs.* PC, collagen/ BC, collagen/ PC	***No MA***; ***periapical healing*** in 2 studies, PC was superior than BC but in 2 other studies there was no sig difference between PC and BC; ***apical closure*** in 2 studies, PC was superior than BC but in 2 other studies there was no sig difference between PC and BC; ***root length*** in 2 studies PC was superior than BC but in 3 studies, there was no sig difference between PC and BC; ***dentinal wall thickness*** in 2 studies, PC was superior than BC but in 2 other studies there was no sig difference between PC and BC
Pryia *et al.* (2023) [23]	RCT (15)	425 (6-54)	Immature	BC, PC, collagen, PLGA, FGF-2	***No MA***; ***overall success rates*** greater effects of PC *vs.* BC (4 papers) and collagen *vs.* BC (1 paper). In three studies there was no sig difference between BC *vs.* PCs; ***pulp vitality*** similar effects between BC and PC (1 paper); ***periapical healing*** similar effects between BC and PC (1 paper). However, in one study there was no sig difference between BC and FGF-2; ***root length*** superior effects of TAP than DAP after RET with BC
Panda *et al.* (2020) [24]	RCT (7)	176 (7-28)	Immature	BC *vs.* APC	***Overall success rates*** no sig difference between BC *vs.* APCs; ***pulp vitality*** superior results in APCs (n=65) than BC (n=56); ***apical closure*** superior results in APCs (n=89) than BC (n=80); ***root length*** no sig difference between APCs (n=74) *vs.* BC (n=65); ***dentinal wall thicknesses*** no sig difference between APCs (n=63) *vs.* BC (n=54); ***calcified barrier formation*** observed in APCs and BC
Yang *et al.* (2024) [25]	RCT (12)	439 (15-28)	Immature	BC *vs.* PCs, BC/FGF-2, Bio-Gide	***Clinical success rates*** no sig difference between BC (n=194) *vs.* other scaffold (n=240); ***pulp vitality*** no sig difference between BC (n=121) *vs.* other scaffold (n=175); ***apical closure*** no sig difference between BC (n=114) *vs.* other scaffold (n=149); ***root length*** no sig difference between BC (n=115) *vs.* other scaffold (n=145); ***dentinal wall thicknesses*** no sig difference between BC (n=104) *vs.* other scaffold (n=134); ***root canal calcification*** no sig difference between BC (n=70) *vs.* other scaffold (n=70)
Sabeti *et al.* (2023) [26]	RCT (9)	290 (8-28)	Immature	BC *vs.* PCs, BC-FGF-2, BC-collagen, PP	***Periapical healing*** greatest results in PC at 1-6m and 6-12m; ***apical closure*** greatest results in PC at 1-6 and 6-12m and BC/collagen beyond 12m; ***root length*** greatest results in PC at 1-6 and 6-12m, and BC/FGF-2 beyond 12m; ***dentinal wall thickness*** greatest results in PC at 1-6 and 6-12m, and BC/collagen beyond 12m
Tang *et al.* (2022) [27]	RCT, Observ (16)	465 (6-28)	Immature	BC *vs.* PC	***Clinical success rates*** no sig difference between BC (n=141) *vs.* PC (n=138); ***pulp vitality*** no sig difference between BC (n=102) *vs.* PC (n=104); ***periapical healing*** superior results for PC (n=134) than BC (n=135); ***apical closure*** no sig difference between BC (n=138) *vs.* PC (n=140); ***root length*** no sig difference between BC (n=71) *vs.* PC (n=80); ***dentinal wall thicknesses*** no sig difference between BC (n=71) *vs.* PC (n=80)
Vatankhah *et al.* (2024) [28]	Observ, CT, RCT (32)	NS (846)	Immature	BC *vs.* PC, collagen membrane, collagen plug	***Clinical success rates*** no sig difference between BC *vs.* PC; ***pulp Vitality*** no sig difference between BC *vs.* PC; ***periapical healing*** no dig difference between BC *vs.* PC; ***dentinal wall thicknesses*** no sig difference between BCs *vs.* PCs; apical closure no sig difference between BC *vs.* PC; ***root length*** no sig difference between BC *vs.* PC; ***discoloration*** in 53% of cases in BC; root canal obliteration in 37% of the cases
Li *et al.* (2023)[29]	RCT (27)	854 (8-30)	Immature /mature	BC *vs.* PC, PP, UC-MSCS,	***Overall success rates*** no sig difference between M (n=178) *vs.* I teeth (n=676); ***pulp vitality*** sig greater results in mature (n=178) than immature teeth (n=676)
Shaik *et al.* (2021) [30]	RCT (10)	321	Immature	Different scaffolds	***NO MA***; ***periapical healing*** present in all cases; ***apical closure*** ranging within 76%–91%; ***root length/ dentinal wall thickness*** 80% to 94%
Ríos-Osorio *et al.* (2023) [31]	RCT (10)	352 (6-40)	Immature	BC *vs.* PC	***No MA***; ***clinical signs/symptoms*** eliminations of sign/symptoms after carrying out different RET with failures in 4 patients; ***periapical healing*** no sig difference between BC *vs.* PC (5 papers). In three papers, PC was superior to BC; pulp vitality no sig difference between PC *vs.* BC (3 papers); ***apical closure*** no sig difference between BC *vs.* PC in 4 studies. However, in 1 study PC has superiority than BC; ***root length*** no sig difference between BC *vs.* PC (3 papers). In three papers, PC was superior to BC; ***dentinal wall thicknesses*** no sig difference between BC *vs.* PC in 4 papers. In another 3 studies, PCs had superiority than BC
Pecci-Lloret *et al.* (2022) [32]	RCT (10)	268 (9-20)	Immature	BC *vs.* PC, BC/ collagen, BC/collagen/ Placentrex, chitosan, FGF-2	***No MA***; ***clinical success rates*** 100% (7 studies), 90% (2 studies), and 80% (1 study); ***pulp vitality*** highest response with PRP, followed by BC/collagen and BC (4 studies); ***root length/dentinal wall thickness*** was evaluated in 7 studied. The best scaffold was PC, followed by BC/collagen, BC and BC/FGF-2

Kharchi *et al.* (2020) [33]	RCT, Obs (5)	70 (7-17)	Immature	NS	***No MA***; ***clinical success rates*** 100% (5 studies); pulp vitality positive response (2 studies); ***periapical healing*** present at 8-12m in (4 studies); ***root length*** increased (5 studies); ***apical closure*** present in 5 studies; dentinal wall thickness increased (5 studies); ***crown discoloration*** present (2 studies); ***partial/complete canal obliteration*** present (3 studies)
Ong *et al.* (2020) [34]	RCT, Obs (11)	282 (8-46)	Immature	BC *vs.* PC	***Survival rates*** 97.3% in 289 patients; ***periapical healing*** 93.0% in 289 patients; ***apical closure*** occurred in 79.1% of cases (n=190); ***root length*** increased in 77.3% of cases (n=258); ***dentinal wall thickness*** increased in 80.6% of cases (n=210)
Alghamdi *et al.* (2020) [35]	RCT, CT, Obs, CR (31)	NS (7-18)	Immature	BC *vs.* PC, PC/FGF-2	***No MA***; ***periapical healing*** observed after using BC or PC in 9 studies; ***apical barrier formation*** presents after application of BC (5 papers); ***apical closure*** occurred after using BC (16 papers), PC (3 papers), or BC/FGF (1 paper); ***root length*** increased after application of BC (4 papers), PC (2 papers), BC/ FGF -2(1 paper); ***dentinal wall thickness*** increased after using BC (10 papers), PC (3 papers), or BC/FGF-2 (1 paper)
Metlerska *et al.* (2019) [36]	RCT (5)	131 (6-28)	Immature	BC *vs.* PC	***No MA***; ***pulp vitality/ apical closure/ root length/ dentinal wall thickness*** greater results in PC than BC
Lolato *et al.* (2016) [37]	CT (4)	61 (10-23)	Immature	BC *vs.* PC	***No MA***; ***pulp vitality*** assessed in one study. 50% of the teeth treated with PC displayed a positive response, against 20% in the control group, with non-sig difference; ***periapical healing*** present in all teeth after 12 or 18 months with no sig difference between BC *vs.* PC; ***apical barrier formation time/ root length/ dentinal wall thicknesses*** greater results of PC than BC; apical barrier formation time no sig difference between BC and PC
Antunes *et al.* (2016) [38]	CR, CS (7)	48 (NS)	Immature	BC *vs.* PC, BC/FGF-2, Colla Core	***No MA***; ***pulp vitality*** positive response in 2 CRs (n=5); ***periapical healing*** present in 5 CRs after RET with BC (n=14). In a CS, healing was occurred in 90.3% of cases (n=16); ***apical closure*** present in 4 CRs after RET with BC (n=18). In a CS, apical closure was occurred in 19.4% of cases (n=16); ***root length*** increased in 1 CR after RET with BC (n=6). In a CS, increasing root length was occurred in 2.7-25.3% of cases (n=16); ***dentinal wall thickness*** increased in 3 CRs after RET with BC (n=12). In a CS, increasing dentinal wall thickness was occurred in 1.9-72.6% of cases (n=16)
Swaikat *et al.* (2023) [39]	RCT, Obs (13)	352 (6-22)	Immature	BC *vs.* PC	***Survival rate*** 93.8% in 384 cases; ***success rate*** 88.3% in 411 cases

APC: *Autologous platelet concentrates;* ***BC:*** *blood cloth;* ***CR:*** *Case reports;* ***CS:*** *Case series;* ***CT:*** *Clinical trials;* ***FGF-2:*** *Fibroblast growth factor-2;* ***MA****: Meta-analysis;* ***N:*** *Number;* ***NRCT:*** *non- Randomized Controlled Trial;* ***NS:*** Not stated; ***Obs:*** *observational studies;* ***PC:*** *Platelet concentrate;* ***PLGA:*** *Poly lactic-co-glycolic acid;* ***PP****: Platelet pellet;* ***PRF:*** *Platelet rich in fibrin;* ***PRP:*** *Platelet rich in plasma;* ***RCT****: Randomized Controlled Trial;* ***RET****: Regenerative endodontic treatment;* ***Sig:*** *significant.*

- Alghamdi *et al.* [35] and Metlerska *et al.* [36] supported the superiority of PRP/PRF over traditional BCs in certain aspects of RETs. However, the quality of evidence varied, and the authors recommended that additional RCTs were needed to confirm these findings.
- Lolato *et al.* compared BCs and PCs and found similar results for pulp vitality and periapical healing, although PCs demonstrated superior outcomes in terms of apical barrier formation time, root length, and dentinal wall thickness [37].
- Antunes *et al.* reviewed RETs using BCs and other scaffolds in case reports/case series and found evidence of root development and periapical healing after RET but did not perform a meta-analysis. They emphasized the need for further research to draw definitive conclusion [38].
- Swaikat *et al.* showed a survival rate of 93.8% in 384 cases and a success rate of 88.3% across 411 cases when comparing BCs to PCs [39].

The current evidence suggests that PCs are promising scaffolds for RETs, offering superior outcome in periapical healing compared to traditional BCs [26, 27]. However, the application of PCs and BCs leads to similar success rates [21, 24, 25, 27, 28]. The evidence regarding outcomes such as pulp vitality, apical closure, and dentinal wall thickness/root length is inconsistent. For pulp vitality, three studies reported no significant difference between PCs and BCs [25, 27, 28], while another study favored PCs [21]. Regarding apical closure, four studies found similar effects [21, 25, 27, 28], while two studies reported greater results with PCs over BCs [24, 26]. Dentinal wall thickness/root length was assessed in five meta-analyses; four studies reported no significant difference between PCs and BCs [21, 24, 25, 27], while another study favored PCs [26]. Overall, the quality of evidence remains limited, and further high-quality studies are needed to strengthen the evidence base.

Bottom Line: The studies on RET indicate that PCs generally outperform BCs in terms of pulp vitality and, in some cases, periapical healing and root development. However, the overall success rates, apical closure, and dentinal wall thickness show mixed results, with no significant differences between PCs and BCs in several studies. PCs tend to offer better outcomes in terms of pulp vitality and root length, but the variability in results suggests that both PCs and BCs can be effective. The findings emphasize the need for standardized protocols and consistent outcome measures to better evaluate the efficacy of different scaffolds in RET.

Table 3. Summary of SR/MA studies comparing RET and apexification

Author (Year)	Design (n)	N (age)	Root Status	RET	Apexification	Key Findings
Panda *et al.* (2022) [21]	RCT, Observ (9)	579 (NS)	Immature	BC, DPSC aggregates	CH, MTA	***Survival rates*** no sig difference between RET (n=331) *vs.* apexification (n=231); ***overall success rates*** no sig difference between RET (n=257) *vs.* apexification (n=252); ***root length/apical foramen width*** no sig difference between RET (n=121) *vs.* apexification (n=66)
Priya *et al.* (2023) [23]	RCT (15)	547 (6-54)	Immature	BC, PC	CH, MTA	***No MA***; ***apical closure/ root length*** in one study superior effect of apexification than RET and in another study similar effects between RET *vs.* apexification was found
Swaikat *et al.* (2023) [39]	RCT (2)	162 (6-22)	Immature	BC/ collagen	CH	***Survival/ overall success rates*** similar results between RET (n=102) *vs.* apexification (n=60); ***apical closure*** similar results between RET(n=102) and apexification (n=60); ***root length/ dentinal wall thickness*** superior results of RET (n=102) than apexification (n=60); ***discoloration*** superior results of RET (n=102) than apexification (n=60)
Stefanidou *et al.* (2024) [40]	RCT (6)	260 (8-46)	Immature	BC, BC/ collagen fiber	CH, MTA	***Root length*** superior effects of RET (n=59) than apexification (n=68); ***dentinal wall thickness*** superior effects of RET (n=89) than apexification (n=44)
Meschi *et al.* (2023) [41]	RCT, NRCT (5)	258 (8-58)	Immature/ mature	UC-MSCs/ Plasma-derived biomaterials/Seal Bio	CH, MTA, root canal therapy	***Survival rates*** no sig difference between RET (n=102) *vs.* Apexification (n=67), with no sig difference between mature *vs.* immature teeth; ***overall success rates*** no sig difference between RET (n=95) *vs.* apexification (n=54), with no sig difference between mature *vs.* immature teeth
Nicoloso *et al.* (2019) [42]	Observ (3)	135 (8-46)	Immature	BC	CH/ MTA	***Overall success rates*** no sig difference between RETs *vs.* apexification
Torabinejad *et al.* (2017) [43]	RCT (10)	998 (8-58)	Immature	BC	MTA	***Survival rates*** no sig difference between RET (n=455) *vs.* apexification (n=543); ***overall success rates*** no sig difference between RET (n=455) *vs.* apexification (n=543); ***apical closure*** 79% in RETs
Widbiller *et al.* (2022) [44]	RCT (2)	124 (NS)	Immature/ mature	UC-MSC/ plasma-derived biomaterial, DPSCs aggregates	CH, MTA, root canal therapy	***No MA***; ***survival rate*** 100% for both treatments; pulp vitality greater response in RET *vs.* apexification or root canal therapy groups; ***blood perfusion*** sig increased in RETs *vs.* apexification or root canal therapy groups; ***periapical healing*** no sig differences between the RET *vs.* root canal therapy (one paper); ***apical closure*** sig higher apical closure in RETs groups *vs.* apexification; ***root length/ dentinal wall thickness*** sig higher results in RETs *vs.* apexification (1 paper)
Tong *et al.* (2017) [45]	RCT, Observ (5)	290 (NS)	Immature	BC, PC	CH/ MTA	***Periapical healing*** no sig difference between MTA plug, BC, or PC; ***apical closure*** sig greater results of RET than MTA plug; with no sig different between BC *vs.* PC; ***dentinal wall thickness/ root length*** sig greater results of RET than apexification; with no sig different between BC *vs.* PC
Xie *et al.* (2021) [46]	RCT (5)	204 (6-20)	Immature	BC, BC/FGF-2, PC	CH, MTA	***Periapical healing*** no sig difference between RET (n=134) *vs.* apexification (n=100); ***apical closure*** no sig difference between RET (n=111) *vs.* apexification (n=78); ***root length*** sig greater result in apexification (n=66) than RET (101); ***dentinal wall thickness*** sig greater result in apexification (n=96) than RET (138)
Kahler *et al.* (2017) [47]	Observ (6)	193 (NS)	Immature	BC, BC/FGF-2 or BC/ Collaplug	CH/ MTA	***No MA***; ***survival rates*** 98.6% for RETs (n=75) and 88.6%. for apexification (n=53); ***clinical success rates*** 89.7% for RETs (n=39) and 100% for apexification (n=12); ***periapical healing*** 89.7% for RETs (n=39) and 100% for apexification (n=8)

BC: *blood cloth; CH: Calcium hydroxide;* ***DPSC:*** *Dental pulp stem cells;* ***MTA:*** *Mineral trioxide aggregates;* ***FGF-2:*** *Fibroblast growth factor-2;* ***MA****: Meta-analysis;* ***NRCT:*** *non- Randomized Controlled Trial;* ***NS:*** *Not stated;* ***Observ:*** *observational studies;* ***PC:*** *Platelet concentrate;* ***RCT****: Randomized Controlled Trial;* ***RET****: Regenerative endodontic treatment;* ***Sig:*** *significant;* ***UC-MSCS:*** *Umbilical cord mesenchymal stem cells.*

iii) RET compared to apexification

- Eleven reviews (3 SRs and 8 SR/MAs) compared the efficacy of RET versus apexification for treating immature/mature teeth with pulp necrosis [21, 23, 39-47] (Table 3). The scaffolds evaluated included BC, PCs, a combination of BC with collagen, collaplug, FGF-2, PC/collagen, MSCs transplantation. The primary outcomes of interest were root development, apical closure, periapical healing, and clinical success.
- Priya *et al.* [23] found inconsistent results in their SR; while RET showed better root development in 1 study, other study highlighted similar efficacy between RET and apexification.
- Swaikat *et al.* [39] and Stefanidou *et al.* [40] found that RET resulted greater root length/dentin thickness compared to apexification. However, Swaikat *et al.* reported similar success rate between these treatment protocols.
- Panda *et al.* [21], Meschi *et al.* [41], Nicoloso *et al.* [42] and Torabinejad *et al.* [43] showed that RET and apexification had similar success in immature teeth over 12 months.
- Widbiller *et al.* [44] found that RET was more effective than apexification in apical closure and increasing root length/dentinal wall thickness, although periapical healing and success rate were comparable. These findings suggest that while RET excels in root development, it does not significantly outperform apexification in inducing healing; however, no meta-analysis was performed.
- Tong *et al.* [45] and Xie *et al.* [46] also reported that RET had superior outcomes in inducing root development compared to apexification while maintaining comparable periapical healing. This reinforces the idea that RET may be the preferred treatment for enhancing root development, although the impact of root development on the overall success rate of treated teeth remains unclear.
- Kahler *et al.* [47] supported the idea that apexification offered greater clinical success and healing compared to RET, but they did not perform a meta-analysis, so the conclusion should be interpreted with caution.

In general, RET demonstrates superior outcomes in root development compared to apexification, while maintaining similar success rates [21, 39, 41-43] and periapical healing [45, 46]. For apical closure, the evidence was inconsistent; two studies reported no sig difference between two treatment protocols [39, 46], while another meta-analysis did [45]. This suggests that RET may be a more favorable treatment option, especially in cases where root development is a primary concern. RET's superiority in promoting root development was particularly evident in immature teeth. However, Meschi *et al.*, found no significant difference in success between mature and immature teeth [41]. Many studies reported that RET had superior outcomes in inducing root development compared to apexification while maintaining comparable clinical success rates. This reinforces the idea that RET may be the preferred treatment for enhancing root development, though the effect of root development on the overall success rate of treated teeth is still unknown.

Bottom Line: Comparative studies of RET versus apexification reveal no significant differences in survival rates or overall success rates between the two treatments. While some studies show superior root length and dentinal wall thickness with RET, others indicate similar outcomes for both RET and apexification. Apical closure is generally better with RET, but results vary. Discoloration and pulp vitality responses also favor RET in some studies. Overall, RET shows promise in terms of root development and vitality preservation, though both approaches appear viable. Continued research with standardized protocols and larger sample sizes is needed to establish definitive advantages and inform clinical decisions.

Comparison of Techniques

When comparing the three approaches, MTA and RET emerged as superior alternatives to CH apexification, primarily due to reduced treatment times and enhanced biocompatibility, while MTA provided a more predictable apical barrier formation, RET showed greater potential for root maturation and the regeneration of vital tissues. However, the lack of standardized RET protocols resulted in variability in clinical outcomes,-highlighting the need for further research to establish uniform guidelines.

Adverse Effects

Adverse effects were most commonly reported with CH apexification, including a higher incidence of cervical root fractures and prolonged treatment duration. MTA was associated with tooth discoloration, which, although non-threatening, posed aesthetic concerns. RET, while promising, exhibited variability in success rates and lacked long-term data to comprehensively evaluate potential complications or adverse effects.

Quality Assessment

A detailed assessment of the included SR/MA using the AMSTAR-2 tool is presented in Table 4. All SRs followed the principles of PICO research questions and inclusion criteria, conducted comprehensive literature searches, and provided essential characteristics of each study. Additionally, all SRs explicitly mentioned that literature screening and data extraction were performed independently by two reviewers. However, only eight studies provided a list of excluded studies. While appropriate tools were used to evaluate the possible risk of bias in the included studies, not all meta-analyses assessed the potential impact of this bias on the outcome measures. Based on Table 4 and the AMSTAR-2 recommended decision rules, the methodological quality has been assessed as "critically low to low", except one rated as high.

Table 4. Results of quality assessment for included SR/MA using the AMSTAR-2 tool

SR/MA	*Q1*	*Q2*	*Q3*	*Q4*	*Q5*	*Q6*	*Q7*	*Q8*	*Q9*	*Q10*	*Q11*	*Q12*	*Q13*	*Q14*	*Q15*	*Q16*	*Rating*
Shaik *et al.*[17]	+	+	+	+	+	+	-	-	-	-	+	-	-	-	-	-	*Critical low*
Nicoloso *et al.*[18]	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	-	*Low*
Lin *et al.*[19]	+	+	+	+	+	+	+	-	+	+	+	-	-	-	+	-	*Critical low*
Chala *et al.*[20]	+	+	+	+	+	+	-	+	+	+	+	+	+	-	-	-	*Critical low*
Panda *et al.*[21]	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	*Low*
Kiaipour *et al.*[22]	+	+	+	+	+	+	-	+	+	-	*NS*	*NS*	-	+	-	-	*Critical low*
Priya *et al.*[23]	+	+	+	+	+	+	-	-	*NS*	-	*NS*	*NS*	-	*NS*	*NS*	-	*Critical low*
Panda *et al.**[24]*	+	+	+	+	+	+	-	+	+	+	+	-	-	-	-	-	*Critical low*
Yang *et al.*[25]	+	+	+	+	+	+	-	+	+	-	+	-	-	-	+	-	*Critical low*
Sabeti *et al.*[26]	+	+	+	+	+	+	-	+	+	-	+	-	-	-	+	-	*Critical low*
Tang *et al.*[27]	+	+	+	+	+	+	-	+	+	+	+	-	-	-	+	-	*Critical low*
Vatankhah *et al.* [28]	+	+	+	+	+	-	+	+	+	-	+	-	-	-	+	-	*Critical low*
Li *et al.*[29]	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	*Critical low*
Shaik *et al.* [30]	+	+	+	+	+	+	-	-	-	-	*NS*	-	-	-	-	-	*Critical low*
Ríos-Osorio *et al.*[31]	+	+	+	+	+	+	-	+	+	+	*NS*	*NS*	-	-	-	-	*Critical low*
Pecci-Lloret *et al.*[32]	+	+	+	+	+	+	-	+	+	+	*NS*	*NS*	-	-	-	-	*Critical low*
Kharchi *et al.*[33]	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	*Critical low*
Ong *et al.*[34]	+	+	+	+	+	+	-	+	+	+	+	-	-	-	-	-	*Critical low*
Alghamdi *et al.*[35]	+	+	+	+	+	+	-	+	+	+	*NS*	*NS*	-	-	-	-	*Critical low*
Metlerska *et al.*[36]	+	+	+	+	+	+	-	+	+	-	+	-	-	-	-	-	*Critical low*
Lolato *et al.*[37]	+	+	+	+	+	+	-	+	+	-	*NS*	*NS*	-	-	-	-	*Critical low*
Antunes *et al.*[38]	+	+	+	+	+	+	-	+	+	-	*NS*	*NS*	-	-	-	-	*Critical low*
Swaikat *et al.*[39]	+	+	+	+	+	+	-	+	+	+	-	-	-	-	-	-	*Critical low*
Stefanidou *et al.*[40]	+	+	+	+	+	+	-	+	+	-	-	-	-	-	-	-	*Critical low*
Meschi *et al.*[41]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	*Low*
Nicoloso *et al.*[42]	+	+	+	+	+	+	+	+	+	-	+	-	+	-	-	-	*Low*
Torabinejad *et al.*[43]	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	*High*
Widbiller *et al.*[44]	+	+	+	+	+	+	+	+	+	+	*NS*	*NS*	+	*NS*	-	-	*Low*
Tong *et al.*[45]	+	+	+	+	+	+	-	+	+	-	+	-	-	+	-	-	*Critical low*
Xie *et al.*[46]	+	+	+	+	+	+	-	+	+	-	+	-	-	-	-	-	*Critical low*
Kahler *et al.*[47]	+	+	+	+	+	+	-	+	-	-	*NS*	*NS*	-	-	-	-	*Critical low*

Q1: Did the research questions and inclusion criteria include PICO components?; **Q2**: Were review methods established prior to the review, with justifications for deviations?; **Q3**: Did the review explain the selection of study designs?; **Q4**: Was a comprehensive literature search strategy used?; **Q5**: Was study selection performed in duplicate?; **Q6**: Was data extraction performed in duplicate?; **Q7**: Did the review provide a list of excluded studies and justify exclusions?; **Q8**: Did the review describe included studies in adequate detail?; **Q9**: Was there a satisfactory technique for assessing risk of bias in individual studies?; **Q10**: Did the review report sources of funding for included studies?; **Q11**: If a meta-analysis was performed, were appropriate statistical methods used?; **Q12**: If a meta-analysis was performed, was the impact of risk of bias assessed?; **Q13**: Was risk of bias accounted for in interpreting/discussing results?; **Q14**: Was there a satisfactory explanation for any observed heterogeneity?; **Q15**: Was publication bias investigated, and its impact discussed? **Q16**: Did the review report potential conflicts of interest and funding sources? **NS** Not stated; **non-critical item;** Q1, Q2, Q5, Q6, Q8, Q10, Q12, Q14, Q16; Critical item; Q3, Q4, Q7, Q69, Q13, Q15

Discussion

The management of immature teeth with pulp necrosis remains a significant challenge in endodontics, with both traditional and contemporary treatment approaches presenting distinct advantages and limitations [48, 49]. This umbrella review synthesizes the current evidence on three main treatment modalities: CH apexification, MTA apexification, and RETs.

Effectiveness and Limitations of CH Apexification

CH apexification has long been the standard treatment for promoting apical closure in immature teeth [50]. Its effectiveness in inducing the formation of a calcified barrier is well-established [20]; however, the technique has drawbacks [51]. The extended treatment duration, often exceeding a year, is a significant disadvantage, particularly for young patients who may struggle with adherence over such a prolonged period [3, 52]. Additionally, the extended application of CH has been associated with an increased risk of cervical root fractures, which can jeopardize the structural integrity and long-term prognosis of the tooth [50]. These limitations underscore the need for more efficient and structurally supportive alternatives.

Advantages and Drawbacks of MTA Apexification

MTA apexification is favored over CH apexification for its reduced treatment time [19]. It typically promotes apical barrier formation within several months, providing a more efficient solution for patients and clinicians [17]. Additionally, MTA supports favorable periapical healing, contributing to the overall success of the treatment [18]. However, MTA does not enhance root development or dentin wall thickness, which are crucial for the long-term structural integrity of the tooth, potentially compromising the treatment's durability [53]. While tooth discoloration with MTA is mainly a cosmetic concern, it may limit its use in aesthetically critical areas, such as the anterior teeth [54-56]. To address this limitation, alternative bioceramic materials like Biodentine and calcium-enriched mixture (CEM) cement, have been explored due to their reduced risk of discoloration [57, 58]. Newer MTA formulations with minimized discoloration potential and the use of barrier materials such as collagen matrices or dentin bonding agents before MTA placement have also been proposed to mitigate staining risks.

Promises and Challenges of RETs

RETs represent a significant advancement in the treatment of immature teeth with pulp necrosis, shifting the focus from mere apical closure to all aspects of root development [21, 23, 39-44, 46, 47, 59]. The ability of RET to promote continued root development and increase dentin wall thickness offers distinct advantages over traditional apexification methods [10]. Platelet concentrates such as PRP and PRF, which are frequently used in RETs, have shown promise in enhancing root length and apical healing, respectively [25-28, 31, 32, 36-38]. However, the success of RETs is currently limited by the absence of standardized protocols. The variability in clinical outcomes observed across studies is likely attributed to differences in procedural techniques, patient selection, and materials used. Consequently, while RETs offer significant potential, widespread adoption necessitates the establishment of standardized treatment guidelines and further research to optimize treatment protocols.

Comparative Analysis and Clinical Implications

When comparing the three approaches, MTA and RETs stand out as superior alternatives to CH apexification, primarily due to their reduced treatment times and higher success rates [21, 23, 40-42, 44, 46]. MTA provides a more predictable apical barrier formation, while RET offers the potential for root maturation and revitalization of the tooth [43]. However, the lack of standardized RET protocols leads to variability in outcomes, highlighting the need for further research to establish uniform guidelines.

Limitations and Future Directions

The included studies exhibit several biases and limitations, including variability in design, sample sizes, and methodologies, which can affect generalizability and consistency. Issues such as inadequate reporting of randomization, potential selection biases, and differences in outcome measurement may influence results. Additionally, publication bias toward positive findings could skew the overall interpretation. These factors highlight the need for more uniform and rigorous research to better assess management strategies for immature teeth with pulp necrosis.

Future research needs to focus on long-term studies of RETs to understand their benefits and limitations better. Standardized protocols are essential for consistent outcomes. Research should aim to establish clear success criteria, explore long-term survival and functionality of treated teeth, and investigate patient-reported outcomes. Comparative studies with traditional apexification in larger, diverse populations are needed. Additionally, the clinical advantage of root development induced by RET remains unclear and should be explored further to assess its true benefits

Conclusion

In conclusion, while CH apexification remains a reliable method, MTA and RETs offer superior alternatives with significant potential for improved outcomes. This umbrella review highlights the significant advancements in the management of immature teeth with pulp necrosis. The findings suggest that RETs offer a promising alternative to traditional apexification techniques, with the potential for better long-term outcomes and revitalizing teeth.

Moving forward, the integration of RETs into mainstream clinical practice will require further refinement of protocols and a deeper understanding of its long-term efficacy. The review underscores the need for future research to focus on standardized outcome measures and long-term follow-up studies, which are essential for establishing the reliability and reproducibility of RET.

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Conflict of interest

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Saeed Asgary: Conceptualization, Writing the Original Draft, and Review/Editing. Sayna Shamszadeh: Cowriting the Original Draft, preparing the Tables and Review/Editing. Ali Nosrat/Anita Aminoshariae/Mohammad Sabeti: Cowriting the Original Draft, and Review/Editing.

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