

Repair before Regeneration: A Scoping Review Mapping Biological Rationale, Clinical Protocols, Outcome Evidence and Translational Frontiers in Regenerative Endodontics

Running title: Regenerative endodontics: a scoping review

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ABSTRACT

Background: Regenerative endodontic procedures (REPs) aim to replace damaged dentine, root structure and cells of the pulp–dentine complex rather than fill the canal with inert material. Their evidence base is large but heterogeneous, spanning laboratory science, case reports, consensus statements and a small number of randomised trials.

Objectives: To map the nature and extent of the evidence on regenerative endodontics; to summarise its biological rationale, clinical protocols, reported outcomes and emerging technologies; and to identify knowledge gaps that should shape future research.

Methods: This scoping review followed the Arksey and O'Malley framework, the Joanna Briggs Institute guidance and the PRISMA-ScR reporting checklist. Sources published between 2011 and 2026 addressing any biological, clinical or translational aspect of regenerative endodontics were eligible. Data were charted on design, focus and principal findings and synthesised thematically.

Results: Twenty-five sources were included: 16 narrative reviews, three systematic or umbrella reviews, two scoping reviews, one structured review of clinical trials, one expert consensus, one bibliometric analysis and one laboratory study. Sixteen were published from 2020 onward. In immature necrotic teeth, reported success ranged from 50% to 98% and survival from 94% to 100%. In mature necrotic teeth with apical periodontitis, pooled randomised data showed no difference from conventional root canal treatment (relative risk 1.03; 95% CI 0.92–1.15). Evidence in irreversible pulpitis was limited to eight case reports and case series. Histological data consistently describe repair tissue of periodontal and osseous origin rather than true pulp–dentine regeneration, and continued root maturation remains unpredictable. Protocols still vary in irrigant concentration, intracanal medicament and dentine conditioning. Translational work centres on nanofibrous, injectable and drug-eluting scaffolds, organoids, tooth-on-a-chip platforms and exosome-based strategies.

Conclusions: REPs are a biologically grounded option for immature teeth with pulp necrosis, but the field rests mainly on low levels of evidence and achieves repair rather than regeneration. Standardised protocols, core outcome sets including patient-centred and histological end points, and adequately powered long-term randomised trials are the main priorities.

Keywords: Regenerative endodontics; Pulp regeneration; Revascularisation; Immature permanent teeth; Tissue engineering; Stem cells

INTRODUCTION

For most of the history of endodontics, a non-vital tooth has had three possible fates: root canal treatment when the apex is mature, apexification when it is not, or extraction [1]. Both conventional approaches succeed in controlling infection, but neither restores living tissue to the root canal space. Non-surgical root canal treatment removes the damaged pulp and replaces it with an inert material such as gutta-percha, and 10–15% of cases may still fail despite advances in technique and materials [2]. Teeth treated in this way are also susceptible to secondary infection and to adverse outcomes such as vertical root fracture [3]. The limitation is most acute in immature permanent teeth, whose open apical foramen and thin dentinal walls make standard root canal treatment difficult to perform and leave the root fragile [4].

Regenerative endodontics emerged as a response to this problem. It has been defined as a set of biologically based procedures designed to replace damaged structures, including dentine and root structure, as well as cells of the pulp–dentine complex [5]. Since the first clinical reports by Iwaya and colleagues in 2001 and by Banchs and Trope in 2004, the European Society of Endodontology and the American Association of Endodontists have issued position statements and clinical considerations, and the approach has been described as a paradigm shift and as a first treatment option for immature teeth with pulp necrosis [6,7]. Conceptually, the field draws on the tissue-engineering triad of stem cells, scaffolds and signalling molecules to re-establish the structure and function of the pulp–dentine complex [8].

The literature has grown rapidly. A scientometric analysis of 694 articles published up to December 2017 found an average yearly growth rate of 40.4% between 2007 and 2017, yet 73.3% of articles were at level of evidence 5 and only 8.3% at level 1 [9]. Clinical protocols evolved empirically, and their heterogeneity has prompted expert consensus statements to guide practitioners [10]. At the same time, recent reviews emphasise that current procedures mainly produce tissue repair rather than true regeneration of a functional pulp–dentine complex, and that protocol standardisation, outcome variability and the gap between laboratory promise and routine practice remain unresolved [11].

Existing reviews in this field tend to address a single domain, such as scaffolds, antimicrobial agents, a particular clinical indication or a particular conditioning agent. A scoping review is well suited to a field of this kind because it maps the extent, range and nature of the evidence across domains and identifies where evidence is thin, rather than answering one narrow effectiveness question. This review therefore aimed to (i) characterise the published evidence on regenerative endodontics by design and focus; (ii) summarise the biological rationale, clinical protocols and reported outcomes; (iii) describe emerging translational strategies; and (iv) identify knowledge gaps and research priorities.

METHODS

Framework and reporting

The review followed the five-stage framework of Arksey and O'Malley [12], as refined in the Joanna Briggs Institute methodological guidance for scoping reviews [13], and is reported according to the PRISMA extension for scoping reviews (PRISMA-ScR) [14]. The stages were: identifying the research question; identifying relevant sources; selecting sources; charting the data; and collating, summarising and reporting the results. [Protocol registration: state the OSF registration number, or state that no protocol was registered.]

Review questions

The guiding question was: *What is the nature and extent of the published evidence on regenerative endodontics, and where are the principal gaps?* Sub-questions addressed (a) the biological basis of REPs; (b) the components and variability of clinical protocols; (c) reported clinical outcomes by indication; and (d) emerging translational technologies.

Eligibility criteria

Eligibility was defined using the Population–Concept–Context framework.

- **Population:** permanent teeth, immature or mature, with pulp necrosis or irreversible pulpitis; human studies, with veterinary sources admitted where they informed clinical translation.
- **Concept:** regenerative endodontic procedures, including revascularisation/revitalisation, cell homing, cell transplantation and scaffold-, biomaterial- or signalling-molecule-based strategies for pulp–dentine regeneration.
- **Context:** any clinical or laboratory setting, published 2011–2026, in English.

- **Source types:** narrative, systematic, umbrella and scoping reviews; meta-analyses; consensus statements; bibliometric analyses; clinical trials; and laboratory studies addressing protocol steps.

Conference abstracts, editorials without original synthesis and sources unavailable in full text were excluded.

Information sources and search

Sources were identified through an electronic search of [PubMed/MEDLINE; add other databases searched] using combinations of the terms and MeSH headings *regenerative endodontics*, *pulp regeneration*, *revascularization*, *revitalization*, *dental pulp necrosis*, *immature permanent teeth*, *tissue engineering* and *stem cells*, supplemented by hand-searching of reference lists. The final search was run on [date]. Records were managed in Zotero reference-management software. [Insert the full search string for at least one database as Supplementary File 1.]

Selection of sources

Two reviewers (M.M.K. and R.K.) screened titles and abstracts independently and then assessed full texts against the eligibility criteria. Disagreements were resolved by discussion, with a third reviewer (N.B.) consulted where needed. [Insert the number of records identified, duplicates removed, records screened, full texts assessed and reasons for exclusion; these populate the PRISMA-ScR flow diagram, Figure S1.] Twenty-five sources met the eligibility criteria and were included.

Data charting and synthesis

A standardised charting form captured first author, year, journal, source type, primary focus, sample or scope (for example, number of included studies) and principal findings relevant to the review questions. Charting was performed by one reviewer and verified by a second. Consistent with scoping-review methodology, formal critical appraisal of individual sources was not undertaken [13]; however, level of evidence was recorded, and the appraisal results reported within included systematic reviews (for example, AMSTAR-2 or Cochrane risk-of-bias judgements) were extracted where available. Findings were collated descriptively and synthesised narratively under four themes: biological rationale, clinical protocol, clinical outcomes and translational frontiers. An evidence-gap map was then constructed by cross-tabulating themes against the highest level of evidence available for each.

RESULTS

Characteristics of the included sources

Twenty-five sources published between 2011 and 2026 were included (Table 1, Figure 1). Sixteen (64%) appeared from 2020 onward, and 2022 was the peak year with four sources. Narrative reviews formed the largest group ($n = 16$; 64%) [1–8,11,15–21]. Formal evidence syntheses comprised one umbrella review [22], one systematic review with meta-analysis [23], one systematic review [24], two scoping reviews [25,26] and one structured review of nine clinical trials [27]. The remaining sources were one expert consensus statement [10], one bibliometric analysis [9] and one laboratory study [28].

The *International Endodontic Journal* [6,17,24,26] and the *Journal of Endodontics* [9,23,25,27] each contributed four sources. One source addressed veterinary practice [5]. Clinical effectiveness data were available only through secondary syntheses, which is itself a finding: the included literature interprets a relatively small pool of primary clinical studies many times over.

Biological rationale

Stem cells and the route to the canal. The included reviews consistently grounded REPs in the tissue-engineering triad of stem cells, scaffolds and signalling molecules [1,2,6,8]. Two strategies for supplying cells were described. *Cell homing* relies on endogenous stem cells that migrate or are carried into the canal, most simply by passive flow within a blood clot induced from the periapical tissues [27]. *Cell transplantation* delivers exogenous cells, such as dental pulp stem cells, into the canal [3,18]. The discovery of dental pulp stem cells gave the field new momentum, and both routes have advanced rapidly in preclinical work [3]. Clinically, however, only cell homing is in routine use, because it avoids the regulatory, manufacturing and logistical burden of cell-based products [11,18,27].

Scaffolds. The blood clot, platelet-rich plasma and platelet-rich fibrin are the scaffolds used in current practice [6,17]. Because none of these reproduces the native pulp extracellular matrix, engineered alternatives have been proposed. Nanofibrous polymer scaffolds produced by self-assembly, electrospinning or phase separation mimic the architecture of pulp extracellular matrix and can carry bioactive molecules, provided they are biocompatible, stable and biodegradable [15]. Such scaffolds are argued to improve the repeatability of regenerative outcomes and to support coordinated formation of connective tissue, dentine, blood vessels and nerves [4].

Signalling molecules and dentine conditioning. Dentine itself is a reservoir of growth factors. A systematic review of 36 laboratory and animal studies found that 15 of 17 studies measuring release reported significant transforming growth factor-beta (TGF- β) release after EDTA conditioning, whereas most found no effect on vascular endothelial growth factor release [24]. EDTA-treated dentine was also associated with greater cell migration, adhesion and differentiation

in vitro. The in vitro evidence carried a low risk of bias, but the animal studies carried a high risk of bias, and no meta-analysis was feasible [24].

The periapical microenvironment. Apical periodontitis interferes with root development in immature teeth, yet the cellular interactions that govern disease and healing remain poorly understood [16]. Two-dimensional monolayer culture cannot represent these interactions; three-dimensional constructs containing mesenchymal stem cells and macrophages offer a closer model of the in vivo environment and allow the role of cytokines to be tested [16]. Residual infection and inflammation are now recognised as major obstacles to regeneration, which has shifted attention towards antibacterial and immunomodulatory microenvironments and to cell-free biological effectors such as exosomes and cell aggregates [18].

Clinical protocol and its variability

The original clinical protocols were empirical, and rapid advances in research have produced substantial variation between practitioners, which the expert consensus identified as a source of confusion in practice [10]. Murray similarly noted that REPs are generating increasingly complex protocols involving revascularisation, autologous platelet-rich plasma and scaffolds, and that success depends on strict adherence to case-selection criteria and precise, monitored steps [17]. Table 2 summarises what the included sources report for each step and what remains unresolved.

The antimicrobial step deserves emphasis, because it is where biology and infection control conflict. Of 16 studies comparing alternatives with triple antibiotic paste, 11 were purely in vitro and only 2 were clinical trials [25]. Antibiotic pastes and filling materials cause tooth discolouration, and endodontic medicaments have been linked to cervical root fracture [15]. Medicament residue is a further concern: in 80 single-rooted teeth prepared to simulate immature roots, none of four irrigation techniques achieved complete removal of calcium hydroxide or double antibiotic paste [28]. Patient-centred consequences, such as discolouration and the need for more appointments, should therefore be discussed with patients and parents before treatment [6].

Clinical outcomes by indication

Three treatment outcomes are recognised for REPs: resolution of clinical signs and symptoms, further root maturation, and return of neurogenesis [6]. The included sources agree that the first is achieved reliably, while the second and third are not. Table 3 summarises the strongest evidence available for each clinical indication.

Immature teeth. This is the indication with the most evidence. The expert consensus cited case reports, case series, cohort studies and randomised studies showing that REPs promote root development [10]. The umbrella review rated three of its 20 included reviews as low methodological quality on AMSTAR-2, and concluded that REPs are supported by high- and moderate-quality literature as a treatment option for necrotic immature teeth [22]. The very wide success range, from 50% to 98%, is itself informative: it reflects differences in protocols, outcome definitions and follow-up rather than a single stable effect.

Mature teeth and irreversible pulpitis. Two newer indications extend REPs beyond their original target. For mature necrotic teeth with apical periodontitis, moderate-certainty evidence suggests REPs are a viable alternative to conventional root canal treatment, although the pooled analysis rested on only three trials and its wide prediction interval (0.51–2.09) leaves future trial results uncertain [23]. Results of cell-homing trials in mature teeth were contradictory [27]. For irreversible pulpitis, the evidence was described as remarkably limited, consisting of eight case reports and case series; the biological rationale is plausible, but vital pulp therapy remains the preferred option [26].

What tissue forms. Histological evidence consistently shows repair derived mainly from periodontal and osseous tissues rather than regeneration of the pulp–dentine complex [6]. The “pulp-like” tissue that forms lacks an odontoblastic layer and does not constitute a true pulp–dentine complex [27]. Several reviews therefore describe current outcomes as repair rather than regeneration [7,11], and note that continued root maturation remains variable even when infection is controlled and the tooth survives [11].

Choosing between options. Traditionally, apexification has been the treatment of choice for immature teeth with necrotic pulp [17]. Current guidance positions REPs as an alternative only when the tooth and patient meet all case-selection criteria, and recommends conventional root canal treatment, Cvek partial pulpotomy, apexogenesis or apexification whenever these are more likely to benefit the patient [17]. Using Cvek’s classification of root development, REPs are proposed for teeth with incomplete root formation, whereas teeth with near or complete root formation may be better suited to conventional therapy or MTA barrier techniques [6].

Translational frontiers

Translational work in the included sources pursued three aims: better infection control without harming stem cells, scaffolds closer to native pulp matrix, and models that predict clinical behaviour.

Drug-delivering scaffolds. Injectable, thermo-responsive and custom 3D-printed scaffolds that carry antimicrobial, anti-inflammatory and signalling cues can deliver drugs within the narrow, branching anatomy of the root canal, combining decontamination with a microenvironment that favours cell migration, adhesion and differentiation [19]. Electrospun fibres offering controlled antibiotic release, and natural antimicrobial compounds, were identified as priorities for investigation [25]. These build on the nanofibrous scaffold concept described earlier [4,15].

Biological effectors and fabrication. Exosomes and cell aggregates have been proposed as biomimetic strategies to establish functional tissue and ease clinical translation [18]. Gene therapy and three-dimensional bioprinting are expected to address current limitations, although both remain at an early stage [8].

Preclinical models. Organoids and multicellular 3D constructs allow high-throughput study of interactions between stem cells and immune cells, including a dental-pulp organoid developed for regenerative endodontics [16]. Tooth-on-a-chip platforms and multifunctional biomaterials were highlighted as routes to clinically relevant testing, with emphasis on strategies that combine angiogenesis, mineralisation and functional tissue formation while limiting immune reaction, infection and necrosis [21].

Beyond the pulp. Regeneration of large periapical bone defects has been framed as a distinct therapeutic target alongside pulp regeneration, driven partly by growing demand for tooth preservation in ageing populations [20]. Veterinary endodontics has adopted REPs as well, drawing on numerous animal studies and case series [5].

Barriers. Widespread adoption of advanced regenerative therapies is limited by the lack of agreed outcome measures and by regulatory, manufacturing and logistical challenges [11].

Evidence-gap map

Table 4 cross-tabulates each theme against the highest level of evidence found and the principal gap. Only clinical outcomes in immature teeth, and to a lesser extent mature necrotic teeth, reached the level of systematic synthesis of clinical data; most biological and translational questions rested on narrative reviews of preclinical work.

DISCUSSION

Principal findings

This scoping review mapped 25 sources spanning 15 years of regenerative endodontics. Four findings stand out. First, the literature is dominated by narrative reviews, and clinical effectiveness is known almost entirely through secondary syntheses of a small pool of primary studies. Second, REPs reliably resolve signs and symptoms and preserve immature teeth, but continued root development and return of sensibility are inconsistent. Third, the tissue that forms is repair tissue of periodontal and osseous origin rather than a regenerated pulp–dentine complex. Fourth, the indications are widening to mature teeth and irreversible pulpitis faster than the evidence that would justify them.

An evidence base that has grown wider rather than deeper

The scientometric profile reported in 2019, in which nearly three-quarters of articles were at level of evidence 5 and fewer than one in ten at level 1 [9], is still recognisable in the sources mapped here. Sixteen of 25 sources were narrative reviews, and they cite overlapping primary studies. This creates an impression of consensus that exceeds the underlying data. The umbrella review found that three of its 20 included reviews were of low methodological quality [22], and the antimicrobial scoping review found only two clinical trials among 16 comparative studies [25]. Even the best clinical estimate for mature teeth rests on three pooled trials [23]. Readers should therefore weigh how often a claim is repeated less heavily than the design of the primary evidence behind it.

Repair versus regeneration

The distinction between repair and regeneration was the most consistent theme across the included sources [6,7,11,27]. It matters clinically for two reasons. First, if the canal fills with cementum-like, bone-like or periodontal-ligament-like tissue, the functional goal is a stronger, longer-surviving tooth rather than a living pulp, and outcomes should be judged accordingly. Second, the wide success range reported in immature teeth, from 50% to 98% [22], probably reflects inconsistent definitions of success as much as true differences in effect. Studies that report “success” without separating symptom resolution, periapical healing, root maturation and sensibility are difficult to compare and cannot show whether regeneration, rather than simple healing, has occurred.

Protocol standardisation

Protocol heterogeneity was identified as a barrier by the expert consensus and by the most recent narrative review [10,11]. The present mapping locates that heterogeneity precisely: case-selection thresholds, irrigant concentration, choice of antimicrobial agent, removal of medicament and use of platelet concentrates all remain unsettled (Table 2). Several of these steps involve a trade-off between disinfection and cell survival. Antibiotic pastes remain highly effective against microorganisms [25], but they cause discolouration [15] and leave residue that current irrigation techniques cannot fully remove [28]. EDTA conditioning is one of the few steps with consistent laboratory support,

through TGF- β release and improved cell behaviour, yet histological confirmation in vivo is still lacking [24]. A core protocol, tested prospectively, would do more for the field than further narrative synthesis.

Expanding indications

The extension of REPs to mature necrotic teeth is supported by moderate-certainty evidence of equivalence to conventional treatment [23], though cell-homing trials in mature teeth are contradictory [27]. Equivalence on a composite success outcome does not, on its own, justify replacing a highly predictable treatment; the argument for REPs in mature teeth must rest on added benefit, such as restored sensibility or defence, which has not yet been shown. For irreversible pulpitis the case is weaker still: eight case-level reports cannot establish effectiveness, and vital pulp therapy remains preferable [26]. These findings support cautious, criteria-based case selection rather than routine use outside immature teeth [17].

Translational outlook

The translational literature has moved from single-component concepts towards multifunctional systems that combine disinfection, immunomodulation and cell guidance [18,19,21]. Better preclinical models, including organoids and tooth-on-a-chip platforms, could reduce the gap between laboratory and clinical results [16,21]. However, cell-based and engineered products face regulatory, manufacturing and logistical hurdles that cell homing avoids [11]. In the near term, the most feasible gains are likely to come from refining cell-homing protocols with better scaffolds and local drug delivery rather than from transplanted cells.

Research priorities

1. Adequately powered randomised trials in immature teeth with standardised protocols and follow-up of at least several years.
2. A core outcome set that reports symptom resolution, periapical healing, root length and wall thickness, sensibility, discolouration and patient-reported outcomes separately.
3. Head-to-head trials of antimicrobial agents and of platelet concentrates versus the blood clot.
4. Comparative studies of REPs against vital pulp therapy in irreversible pulpitis and against conventional treatment in mature teeth, powered for outcomes beyond survival.
5. Human histological series and validated in vivo models to establish what tissue forms and why.
6. First-in-human studies of engineered, drug-eluting scaffolds within a clear regulatory pathway.

Strengths and limitations

This review covers the full spectrum from biology to clinical outcomes and translational technology, and presents an explicit evidence-gap map. Several limitations apply. The review was restricted to English-language sources, and its findings depend on the completeness of the search. Most included sources were secondary, so primary studies were represented indirectly and some may be counted more than once across reviews. In line with scoping-review methodology, individual sources were not critically appraised, and the review does not estimate treatment effects. Finally, charting relied on the reporting of included sources, which varied in detail.

CONCLUSIONS

Regenerative endodontics is a biologically grounded and clinically useful option for immature permanent teeth with pulp necrosis, where it resolves infection, preserves the tooth and, in many cases, allows root development to continue. Its evidence base, however, is broad rather than deep: it is dominated by narrative reviews, relies on a limited number of primary clinical studies, and documents repair rather than true regeneration of the pulp–dentine complex. Use in mature necrotic teeth is supported by moderate-certainty evidence of equivalence, whereas use in irreversible pulpitis remains experimental. Progress now depends less on new biomaterials than on standardised protocols, agreed outcome measures and long-term randomised trials.

Declarations

Author contributions: Conceptualisation, M.M.K.; methodology, M.M.K. and R.K.; screening and data charting, M.M.K. and R.K.; adjudication and periodontal and periapical perspectives, N.B.; writing – original draft, M.M.K.; writing – review and editing, R.K. and N.B. All authors approved the final manuscript.

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Data availability: The data-charting form and extracted data are available from the corresponding author on reasonable request.

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Table 1. Characteristics of the included sources (n = 25), in order of citation.

Ref.	First author, year	Source type	Primary focus	Principal finding relevant to this review
1	Bansal, 2011	Narrative review	Revascularisation and tissue engineering	Framed restoring vitality as the alternative to RCT, apexification or extraction; set out hurdles to development
2	Dhillon, 2016	Narrative review	Concepts, protocol, research avenues	10–15% of conventional RCT may fail; outlined revascularisation, scaffold-aided regeneration and pulp implantation
3	Luo, 2024	Narrative review	Cell transplantation and cell homing	RCT-treated teeth prone to reinfection and vertical root fracture; DPSC discovery accelerated the field
4	Huang, 2022	Narrative review	Nanofibrous scaffolds	Nanofibres may improve repeatability and support coordinated regeneration
5	Feigin, 2017	Narrative review (veterinary)	REPs in animal patients	Over 80 case reports in a decade; terminology, case selection and procedural details unresolved
6	Kim, 2018	Comprehensive review	Outcomes and future directions	Three outcome goals; histology shows repair from periodontal and osseous tissue; REPs best suited to incomplete root formation
7	Pulyodan, 2020	Narrative review	Current clinical protocols	Current protocols achieve repair rather than true regeneration
8	Alothman, 2024	Narrative review	Stem cells, scaffolds, signalling, gene therapy, bioprinting	Variable outcomes; standardised protocols needed
9	Shamszadeh, 2019	Bibliometric analysis	Research output to 2017	694 articles; 40.4% yearly growth; 73.3% at LOE 5, 8.3% at LOE 1
10	Wei, 2022	Expert consensus	Biology, protocols, complications	Protocol heterogeneity addressed with consensus guidance
11	Risso, 2026	Narrative review	Protocols, prognosis, emerging therapies	Root maturation variable; repair not regeneration; regulatory and manufacturing barriers
15	Kaushik, 2016	Narrative review	ECM-mimicking nanofibre microenvironments	Five unresolved challenges, including discolouration, cervical fracture and absent vascularisation and innervation
16	Li, 2023	Narrative review	3D culture models and organoids	3D multicellular models capture stem cell–macrophage crosstalk better than 2D culture
17	Murray, 2023	Narrative review (guidance)	Treatment selection for immature teeth	Strict case selection; conventional options preferred where more likely to succeed
18	Shi, 2025	Narrative review	Bench-to-clinic translation	Residual infection and inflammation are key hurdles; exosomes and cell aggregates promising
19	Dos Reis-Prado, 2025	Narrative review	Optimising regenerative methods	Injectable, thermo-responsive and 3D-printed drug-carrying scaffolds
20	Kyaw, 2025	Narrative review	Pulp and periapical bone regeneration	Regeneration strategies for pulp function and large apical bone defects

Ref.	First author, year	Source type	Primary focus	Principal finding relevant to this review
21	Soares, 2021	Narrative review	Multifunctional biomaterials, tooth-on-a-chip	Current treatments lack functional, predictable pulp regeneration
22	Rojas-Gutiérrez, 2022	Umbrella review	Effectiveness and success factors	20 reviews (13 SRs, 7 MAs); success 50–98%, survival 94–100%; 3 of low quality on AMSTAR-2
23	Glynis, 2021	SR with meta-analysis	REPs vs RCT in mature necrotic teeth	4 RCTs, 3 pooled; RR 1.03 (95% CI 0.92–1.15); moderate-quality evidence
24	Dos Reis-Prado, 2022	Systematic review	EDTA dentine conditioning	36 studies; 15 of 17 found TGF-β release; improved cell migration, adhesion and differentiation in vitro
25	Ribeiro, 2020	Scoping review	Alternatives to triple antibiotic paste	16 studies, 2 clinical; TAP remains highly effective; electrospun fibres and natural compounds merit study
26	Torabinejad, 2026	Scoping review	REPs in irreversible pulpitis	6 case reports and 2 case series; vital pulp therapy remains preferable
27	Yan, 2023	Structured review of clinical trials	Cell homing	9 trials; favourable in immature teeth, contradictory in mature teeth
28	Usta, 2024	Laboratory (ex vivo) study	Removing medicaments by irrigation activation	80 teeth; SWEEPS most effective, needle irrigation least; no technique achieved complete removal

Abbreviations: DPSC, dental pulp stem cell; ECM, extracellular matrix; LOE, level of evidence; MA, meta-analysis; RCT, root canal treatment (rows 1–3) or randomised controlled trial (row 23); RR, relative risk; SR, systematic review; SWEEPS, shock wave-enhanced emission photoacoustic streaming; TAP, triple antibiotic paste; TGF-β, transforming growth factor-beta. References 12–14 are methodological and are not included sources.

Table 2. Steps of a regenerative endodontic procedure: reported practice and unresolved questions.

Protocol step	What the included sources report	Unresolved question	Ref.
Case selection	Best suited to immature teeth with pulp necrosis and incomplete root formation; teeth with near or complete root formation may be better served by conventional therapy or an MTA apical barrier	Which mature or near-mature teeth benefit	6, 17
Irrigation and disinfection	Disinfection must control infection while preserving stem cell viability; 1.5% NaOCl followed by saline used in a laboratory model of the protocol	Optimal irrigant, concentration and activation	11, 28
Intracanal medicament	Triple antibiotic paste remains highly effective; modified TAP, double antibiotic pastes, propolis, chlorhexidine and Ca(OH) ₂ perform broadly similarly, the last two of doubtful value for infection control	Choice and concentration of agent	25
Medicament removal	No irrigation technique removed Ca(OH) ₂ or DAP completely; SWEEPS removed most, needle irrigation least	Effect of residue on stem cells	28
Dentine conditioning	17% EDTA releases TGF-β and improves cell behaviour in vitro	Confirmation in histological in vivo studies	24, 28
Scaffold	Induced periapical bleeding; platelet-rich plasma or platelet-rich fibrin	Whether platelet concentrates outperform the blood clot	6, 17
Coronal seal	A well-sealed coronal restoration is a prerequisite for success	—	11
Follow-up	Clinical and radiographic review against defined success criteria; follow-up in the literature ranges from 1 to 48 months	Minimum follow-up and core outcome set	17, 22

Abbreviations: DAP, double antibiotic paste; EDTA, ethylenediaminetetraacetic acid; MTA, mineral trioxide aggregate; NaOCl, sodium hypochlorite; SWEEPS, shock wave-enhanced emission photoacoustic streaming; TAP, triple antibiotic paste; TGF- β , transforming growth factor-beta.

Table 3. Clinical outcomes of regenerative endodontic procedures by indication, from the highest level of evidence among the included sources.

Indication	Highest evidence among included sources	Principal findings	Ref.
Immature permanent teeth with pulp necrosis	Umbrella review of 20 reviews (13 systematic reviews, 7 meta-analyses)	Success 50–98%; survival 94–100%; follow-up 1–48 months; outcomes included symptom resolution, periapical healing, root lengthening, dentine thickening and recovery of sensibility	22
Immature teeth, cell-homing approach	Structured review of 9 clinical trials	Favourable results in immature teeth	27
Mature teeth with pulp necrosis and apical periodontitis	Systematic review and meta-analysis of randomised trials (4 included, 3 pooled)	No difference from conventional treatment: RR 1.03 (95% CI 0.92–1.15; $P = .61$; $I^2 = 0\%$); prediction interval 0.51–2.09; moderate certainty	23
Mature teeth, cell-homing approach	Structured review of 9 clinical trials	Contradictory results	27
Immature teeth with irreversible pulpitis	Scoping review	4 case reports describing moderately successful pulp regeneration	26
Mature teeth with irreversible pulpitis	Scoping review	2 case series and 2 case reports with comparable outcomes; vital pulp therapy preferred	26

Abbreviations: CI, confidence interval; RR, relative risk.

Table 4. Evidence-gap map of regenerative endodontics derived from the included sources.

Theme	Topic	Highest level of evidence identified	Principal gap	Ref.
Biology	Cell homing vs cell transplantation	Narrative reviews of preclinical and early clinical work	Human comparative data on cell transplantation	3, 18, 27
Biology	Dentine conditioning and growth factor release	Systematic review of in vitro and animal studies	Histological studies in immature-tooth models	24
Biology	Immune and periapical microenvironment	Narrative reviews; 3D in vitro models	Validated in vivo models	16, 18
Protocol	Antimicrobial agent	Scoping review including 2 clinical trials	Head-to-head randomised trials of agents	25
Protocol	Medicament removal	Single ex vivo study	Effect of residue on clinical outcome	28
Protocol	Standardisation	Expert consensus	Agreed core protocol and core outcome set	10, 11
Outcomes	Immature necrotic teeth	Umbrella review	Long-term randomised trials; sensibility and patient-reported outcomes	22, 27
Outcomes	Mature necrotic teeth	Meta-analysis of 3 randomised trials	Larger trials with longer follow-up	23, 27
Outcomes	Irreversible pulpitis	Case reports and case series	Any comparative study against vital pulp therapy	26
Outcomes	Nature of tissue formed	Human and animal histology summarised in reviews	Systematic human histological series	6, 27
Translation	Engineered and drug-eluting scaffolds	Narrative reviews of preclinical work	First-in-human trials	4, 15, 19
Translation	Organoids, tooth-on-	Narrative reviews	Validation and regulatory	8, 16, 18,

Theme	Topic	Highest level of evidence identified	Principal gap	Ref.
	a-chip, exosomes, bioprinting, gene therapy		pathways	21
Translation	Periapical bone regeneration	Narrative review	Clinical studies	20

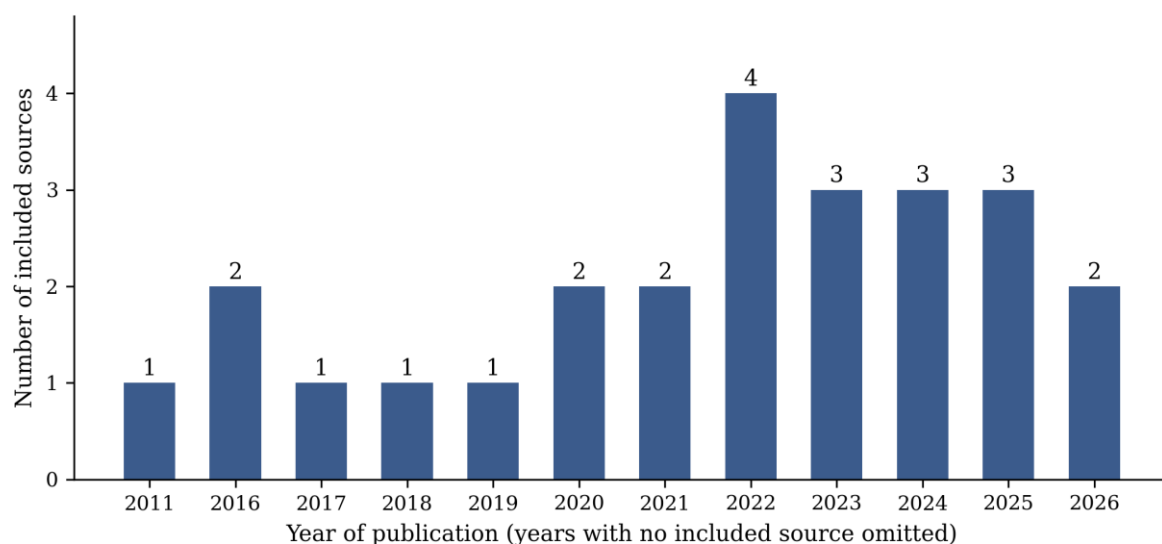


Figure 1. Distribution of the 25 included sources by year of publication. Sixteen sources (64%) were published from 2020 onward; years with no included source are omitted.