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Beyond irreversible pulpitis: Redefining vital pulp therapy through a tissue-response-based paradigm

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Abstract: For decades, diagnosing *irreversible pulpitis* (IP) has driven routine root canal treatments, despite increasing evidence that inflamed vital pulps still possess significant regenerative capacity. This review integrates epidemiological, clinical, and biological data to establish a tissue-response model centered on pulp viability and healing potential. Symptom-based diagnosis often misclassifies cases, leading to overtreatment; therefore, the traditional binary terminology (reversible vs. irreversible) should be replaced with a spectrum-based classification (mild, moderate, severe pulpitis), necessitating an urgent update of endodontic guidelines. Histological studies confirm that pulp healing can occur despite inflammation, while high-quality evidence from randomized controlled trials demonstrates the success of vital pulp therapy (VPT), achieving high success rates in teeth previously labeled as having *IP*. Calcium silicate-based biomaterials (e.g., MTA, CEM cement, Biodentine) support angiogenesis and regeneration of the dentin-pulp complex even in severely inflamed pulps. Factors predicting treatment success include the degree of pulpal inflammation, the type of final restoration, and the presence of apical periodontitis before treatment. By combining insights from biomaterial science, regenerative biology, and clinical trials, this review advocates a tissue-response model that emphasizes pulp healing capacity over static histological labels. This change promotes VPT as the primary treatment for inflamed pulps, prompts an immediate revision of endodontic terminology and guidelines, and establishes a regenerative, minimally invasive approach as the standard for modern endodontic care. Nevertheless, current limitations—including diagnostic uncertainty, lack of standardized protocols, and limited high-level evidence—highlight the need for further refinement before universal adoption.

Keywords: *CEM cement, Calcium silicate cement, Dental pulp, Mineral trioxide aggregate, Pulp capping, Pulp regeneration, Pulpitis, Pulpotomy, Primary molar, Regenerative endodontics, Tissue-response paradigm, Tooth resorption, Vital pulp therapy.*

1. Introduction

The Glossary of Endodontic Terms [1] defines pulpitis as inflammation of the dental pulp, with clinical categories of *reversible* vs. *irreversible pulpitis (IP)*, and histological descriptors of *acute, chronic, or hyperplastic* [1]. Within this framework, *reversible pulpitis* is considered capable of resolution. In contrast, IR [whether symptomatic (lingering thermal or spontaneous pain, referred pain) or asymptomatic (caries-/trauma-induced inflammation without symptoms)] is defined as a state where the vital inflamed pulp is incapable of healing. Chronic hyperplastic pulpitis (pulp polyp) is categorized separately under hyperplastic variants.

This binary model has dominated endodontic diagnosis and treatment for decades, dictating that teeth diagnosed with IP undergo immediate root canal treatment (RCT) [1]. The assumption that an "incapable of healing" pulp is biologically terminal has entrenched a deterministic treatment pathway, leading to widespread pulpectomy and RCT. However, mounting scientific evidence exposes a profound gap between these definitions and clinical reality. Epidemiological data indicate widespread overtreatment, while translational research consistently demonstrates that inflamed vital pulps, previously labeled as

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irreversible, retain significant healing and regenerative capacity when treated with biologically oriented vital pulp therapy (VPT) [2].

The critical weaknesses of the current classification lie in its *static histopathological determinism* and *symptom-driven subjectivity*. First, histological-clinical discordance is well documented: pulps diagnosed as irreversible frequently contain viable tissue with intact reparative mechanisms and putative stem cells [3-5]. Second, diagnostic reliance on symptoms such as lingering pain lacks predictive reliability; it is revealed that pulps diagnosed with symptomatic IP demonstrate histological and clinical healing capacity [6-9]. Third, the biological resilience of the pulp, its ability to mount controlled inflammation, resolve infection, and stimulate angiogenesis and dentinogenesis when protected by advanced biomaterials, contradicts the "incapable of healing" doctrine [5, 10].

Systematic reviews and multicenter randomized controlled trials provide compelling high-level evidence that the full spectrum of VPTs, including indirect pulp capping, direct pulp capping, miniature pulpotomy, partial pulpotomy, full pulpotomy, and partial pulpectomy, achieves favorable outcomes even in permanent teeth diagnosed with IP [11-13]. Reported long-term success rates consistently range between 89% and 95%, outcomes that rival or exceed those of conventional RCT while preserving pulp vitality and natural defense mechanisms [2]. Critically, VPT demonstrates superior cost-effectiveness, reducing treatment expenses compared to RCT while minimizing tooth structure loss and long-term biomechanical complications [14, 15]. This remarkable efficacy is closely attributed to the advent of calcium silicate-based biomaterials (CSBs) such as mineral trioxide aggregate (MTA), calcium-enriched mixture (CEM) cement, and Biodentine [16]. These biomaterials provide not only durable and biocompatible seals in challenging clinical environments but also act as active biological modulators: they release calcium and hydroxyl ions [17-19], promote odontoblastic differentiation [20, 21], upregulate angiogenic signaling pathways [22, 23], and foster dentin-pulp complex regeneration even in severely inflamed tissues [24, 25]. Such findings decisively challenge the Glossary of Endodontic Terms' assertion that an inflamed pulp is "incapable of healing." Instead, they demonstrate that when microbial control is established and pulpal tissue is sealed with bioactive biomaterials, regenerative capacity persists across all VPT modalities [11]. Collectively, this evidence dismantles the historical dogma of IP and mandates a paradigm shift in diagnosis and treatment, from extirpation-based approaches toward biologically driven, minimally invasive therapies centered on tissue preservation and healing [26].

Collectively, the emerging evidence mandates a conceptual shift: pulpitis should be understood not as a binary endpoint but as a dynamic continuum (mild, moderate, severe), where outcomes are governed by microbial control, host immune response, and biomaterial-driven regeneration. This review synthesizes epidemiological, clinical, and biological evidence to argue for replacing the outdated IP terminology with biologically accurate descriptors and to establish VPT as the first-line treatment for vital inflamed pulps in modern endodontic practice.

The proposed tissue-response paradigm rests on three interdependent pillars: 1) biomaterial-driven regeneration, 2) high-level clinical evidence, and 3) histological and translational validation. Together, these strands dismantle the traditional concept of IP and establish biological viability, not symptomatology or static histology, as the cornerstone of modern endodontic decision-making.

1.1. Biomaterials as Catalysts for Regeneration

The advent of MTA, CEM cement, Biodentine, and other evidence-supported CSBs has fundamentally transformed the therapeutic landscape of VPTs [16, 27-29]. Unlike earlier medicaments such as calcium hydroxide, CSBs exhibit true bioactivity: they are biocompatible, hydrophilic, and regenerative, enabling successful management of even severely inflamed pulps.

Mechanistically, CSBs orchestrate pulp healing through three complementary pathways. First, *angiogenesis* is induced through hypoxia-inducible factor-1α (HIF-1α) stabilization, which upregulates vascular endothelial growth factor (VEGF) expression and activates Phosphoinositide 3-Kinase (PI3K)/Protein Kinase B (Akt)/mammalian Target of Rapamycin (mTOR) signaling pathways. This stimulates endothelial tip cell migration, lumen formation, and pericyte recruitment, establishing

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functional microvasculature within the inflamed pulp. The resulting neovascularization restores oxygen/nutrient supply and removes metabolic waste, creating a regenerative-permissive niche[30, 31]. Second, *immunomodulation* establishes a pro-regenerative microenvironment where CSBs release bioactive ions that induce transforming growth factor-β1 (TGF-β1) and interleukin-10 (IL-10) secretion, suppress Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB) activation, and drive macrophage polarization from pro-inflammatory M1 to reparative M2 phenotypes, accelerating inflammation resolution and tissue repair [32, 33]. Beyond these established mechanisms, future-oriented translational strategies such as exosome-mediated signaling, cell aggregates, and biomimetic scaffolds are increasingly recognized as powerful adjuncts to create antibacterial and immunomodulatory microenvironments that enhance pulp-dentin complex regeneration [33]. This positions immunomodulation not only as a central mechanism of current bioactive materials but also as a critical frontier linking infection control, inflammation resolution, and next-generation tissue-engineering approaches. Third, *dentinogenesis* is initiated by sustained calcium and phosphate ion release, creating supersaturated microenvironments that nucleate hydroxyapatite crystallization. These ions activate bone morphogenetic protein-2 (BMP-2)/Smad signaling cascades, triggering nuclear translocation of Runt-related transcription factor 2 (Runx2) and Osterix transcription factors. This upregulates dentin sialophosphoprotein (DSPP) and dentin matrix protein-1 (DMP-1), driving odontoblastic differentiation of resident pulp stem cells and stimulating three-dimensional dentin bridge formation with tubular structure [34, 35].

1.2. Clinical Evidence: VPT Success in IP

High-quality evidence from randomized controlled trials demonstrates that VPTs are highly effective in treating primary/permanent teeth diagnosed with IP [2, 36-38]. A recent systematic review analyzed 12 studies, including 9 randomized controlled trials and 3 prospective cohort studies, evaluating VPT using CSBs such as MTA, CEM, and Biodentine in permanent posterior teeth. Reported success rates ranged from 78% to 90% at one to five years post-treatment, with radiographic success rates between 81% and 90% [39]. Multicenter randomized controlled trials directly comparing VPT with RCT found equivalent outcomes at one-, two, and five-year follow-ups [40-43], supporting VPT as a viable, less invasive alternative in carefully selected cases; these provide robust long-term evidence for mature permanent teeth presenting with spontaneous pain. Pulpotomy with CEM cement achieved a cumulative success rate of 92% at five years, while MTA pulpotomy demonstrated comparable success (89–90%) over three to five years [39]. These findings collectively confirm that, with proper case selection and application of CSBs, VPT can reliably preserve pulp vitality even in teeth traditionally classified as having IP. Importantly, VPT is no longer considered experimental; it has reached guideline-level evidence, with multiple professional organizations now recommending it as a first-line option for managing IPs.

Clinical selection among miniature, partial, and full pulpotomy is typically guided by the degree of pulpal inflammation, radiographic caries depth, and size of pulp exposure [11](Table 1). Miniature pulpotomy (removal of ~1 mm of pulp tissue) is often appropriate for mild inflammation with pinpoint exposures [11, 44, 45], whereas partial pulpotomy (2–3 mm removal) is favored in moderate inflammation with small but definite exposures [11, 46]. Full pulpotomy is generally indicated in severe inflammation or when carious destruction results in broad exposures [11, 47-49]. Despite high success across all modalities with CSBs, the absence of standardized protocols for pulpal tissue removal depth complicates direct comparisons across studies.

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Table 1.
Clinical Guide for Pulpotomy Selection.

Pulpotomy Type	Tissue Removal Depth	Typical Indications	Notes
Miniature Pulpotomy	~1 mm	Mild pulp inflammation; deep caries with pinpoint exposure	Conservative option; high success with CSBs when a hermetic seal is achieved.
Partial Pulpotomy	2–3 mm	Moderate inflammation; small but definite pulp exposure in deep or extremely deep caries	Balances tissue removal and preservation; widely used with CSBs.
Full Pulpotomy	Total coronal pulp removal	Severe inflammation; broad pulp exposure in extremely deep caries	Indicated when exposure is large or inflammation is extensive; preserves radicular pulp vitality.

Hemostasis, traditionally viewed as a determinant of pulpotomy extent, has also undergone critical reappraisal. American Academy of Pediatric Dentistry (AAPD) guidelines recommend hemostasis within a few minutes, and some protocols have historically escalated treatment when bleeding persisted beyond 2–5 minutes. However, recent meta-analyses and large cohort studies demonstrate no significant association between hemostasis duration and long-term VPT success [50, 51], suggesting that prolonged bleeding does not mandate more aggressive pulp removal, i.e., RCT [52]. Instead, outcomes remain comparable across different bleeding-time categories, indicating that hemostasis should be considered a secondary prognostic factor. Treatment decisions are more reliably informed by exposure size, caries depth, and overall inflammation severity rather than bleeding duration alone [53, 54].

A recent retrospective cohort study of 1257 VPT-treated teeth with over 10 years of follow-up reported survival and success rates of 99.1% and 91.6%, respectively, with comparable outcomes across direct pulp capping (91.9%), miniature pulpotomy (92.6%), and full pulpotomy (90.1%) [50]. Critical predictors of failure included symptomatic IP (HR 1.97, 95% CI 1.24–3.14; P = 0.004), radiographic evidence of apical periodontitis (HR 2.98, 95% CI 1.96–4.54; P < 0.001), and unfavorable restorative factors such as composite resin restorations (HR 2.26, 95% CI 1.42–3.60; P = 0.001) or multiple restoration surfaces (HR 1.40, 95% CI 1.03–1.90; P = 0.030) [50]. Complementing these findings, a 7-year retrospective analysis of cariously exposed permanent teeth diagnosed with IP reported overall success and survival rates of 88.2% and 97.1%, respectively, with partial pulpotomy demonstrating the highest success (92.0%) and survival time compared to direct pulp capping (87.7%) and full pulpotomy (87.7%) [55]. Multivariate analysis identified periapical radiographic lesions, type of pulp dressing material, and final restoration quality as the most significant predictors of success [55]. Collectively, these data indicate that periapical status, pulpal inflammation severity, and restorative integrity are the true determinants of VPT outcomes, while clinical symptoms such as spontaneous or lingering pain are not reliable prognostic markers.

1.3. Histological and Translational Validation

Histological and translational research consistently demonstrates that inflamed pulps retain significant regenerative capacity, directly contradicting the conventional "irreversible" designation. Multiple histological investigations have confirmed that inflamed pulps usually contain vital tissue with preserved vasculature and innervation, even when diagnosed clinically as IP [4, 9, 56]. Moreover, mesenchymal stem/progenitor cell markers such as STRO-1, CD90, and CD146 have been localized in inflamed pulpal tissue, confirming the persistence of regenerative niches within perivascular regions [5, 57].

Evidence from human teeth treated with VPT further substantiates this regenerative potential. Histological sections demonstrate reparative dentin bridge formation, recruitment of odontoblast-like cells expressing DSPP and DMP1, and robust angiogenesis mediated by VEGF and angiopoietins [58, 59]. Importantly, these findings reveal that inflammation and regeneration are not mutually exclusive

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processes but often coexist, enabling continued pulp healing when appropriate biological conditions are established [60].

Molecular studies provide mechanistic insight into these phenomena. Early phases of repair are characterized by suppression of NF-κB–driven proinflammatory signaling, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), mediated in part by immunoregulatory cytokines such as TGF-β1 and IL-10 [59, 60]. Subsequently, odontogenic pathways including BMP-2, RUNX2, and Canonical Wnt signaling pathway (Wnt/β-catenin) are activated, promoting odontoblast differentiation and dentinogenesis [59, 61, 62]. In later stages, angiogenic and neurogenic signaling is upregulated, with VEGF and angiopoietin-1/Tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (Tie2) pathways driving neovascularization and tissue reinnervation [10, 23]. New evidence further suggests that autophagy-related pathways enhance odontoblastic differentiation under inflammatory stress, highlighting the pulp's adaptive resilience [60].

Collectively, these histological and molecular data reveal the central paradox of the current diagnostic framework: pulps labeled as "irreversible" frequently retain viable stem/progenitor niches, demonstrate regeneration of the dentin-pulp complex under CSBs, and exhibit consistent suppression of destructive inflammatory cascades. When bacterial insult is eliminated and the pulp is sealed within a bioactive microenvironment, regeneration reliably proceeds, underscoring that the term IP does not reflect the true biological potential of the inflamed pulp. A recent systematic review and meta-analysis further demonstrated that pulps diagnosed clinically with symptomatic IP exhibit significantly increased expression of IL-8, TNF-α, MMP-9, and Receptor for Advanced Glycation End-products (RAGE), underscoring the molecular complexity of pulpal inflammation beyond symptom-based labels [63].

2. Discussion

The evidence synthesized in this review demonstrates that the conventional paradigm of IP as a biologically terminal condition is no longer tenable. The static, symptom-driven classification that has guided endodontic decision-making for decades is reductionist and fails to reflect the biological resilience of the pulp. Histological investigations consistently show that clinically diagnosed IP retains viable pulp tissue, preserved vasculature, and stem/progenitor niches with regenerative potential. Clinical reliance on symptoms such as spontaneous or lingering pain is diagnostically unreliable, with little correlation to actual healing capacity [9]. Recent meta-analytic evidence further supports this diagnostic ambiguity, as elevated expression of IL-8, TNF-α, MMP-9, and RAGE was consistently found in teeth clinically diagnosed with IP, reinforcing that symptom-based categories do not reliably capture biological reality [63]. These findings establish that vitality, not symptomatology, is the true determinant of pulpal prognosis. However, it must be acknowledged that clinical/histological studies remain heterogeneous in methodology and case selection, limiting the strength of direct correlations between diagnostic categories and treatment outcomes.

High-level clinical evidence provides strong support for this reconceptualization, although outcomes must be interpreted within the context of study heterogeneity. Multiple multicenter randomized controlled trials, long-term cohort studies, and systematic reviews demonstrate that VPTs achieve success rates of 85–95% in pulps diagnosed as IP. Importantly, outcomes are comparable to or even exceed those of conventional RCT, while preserving pulp vitality and natural immune and sensory functions. Nonetheless, reported success rates vary depending on operator expertise, biomaterial selection, follow-up duration, and patient-related factors, underscoring the importance of cautious generalization. VPTs are therefore not experimental but firmly established at the level of guideline-supported therapy, with professional organizations now recommending pulpotomy and related procedures as first-line treatments in vital inflamed pulps. This transition reflects not only therapeutic efficacy but also cost-effectiveness, structural preservation, and reduction of treatment burden for patients.

At the biological level, CSBs provide the mechanistic foundation for this paradigm shift. By orchestrating angiogenesis, immunomodulation, and dentinogenesis, these biomaterials transform the

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inflammatory microenvironment into one conducive to regeneration. Importantly, inflammation and regeneration are not mutually exclusive; rather, controlled inflammatory signaling appears to prime reparative pathways, activating odontoblast differentiation and promoting angiogenesis and reinnervation. This biological resilience explains why pulps historically deemed "incapable of healing" can, under appropriate biomaterial-mediated conditions, regenerate structurally and functionally.

Nevertheless, several challenges remain before full clinical translation is achieved. First, diagnostic ambiguity persists: current classifications remain symptom-based and reductionist, while histological and molecular evidence support a continuum-oriented, biology-based system. Updating international guidelines to reflect a tissue-response model is therefore urgently needed. Second, prognostic heterogeneity requires refinement. While factors such as the presence of apical periodontitis, restoration quality, and biomaterial selection consistently predict outcomes, clinical symptoms are poor prognostic markers. The development of biologically anchored diagnostic tools, such as molecular biomarkers or advanced imaging, may enhance precision in case selection. Third, long-term follow-up data beyond 10 years remain limited, and standardization of outcome measures is lacking across trials. Patient-reported outcomes, cost-effectiveness analyses, and assessment of long-term tooth survival in functional dentition should be prioritized in future research.

The role of bleeding duration during VPTs remains debated and requires cautious interpretation. While the ability to achieve hemostasis has historically been regarded as a marker of pulpal health, emerging clinical evidence suggests that bleeding duration alone is not an independent predictor of VPT success [50, 55]. Rather, it should be contextualized alongside factors such as exposure size, caries depth, and overall inflammation severity. Prolonged bleeding may indeed reflect heightened vascularity and inflammatory activity, which in some cases could coexist with regenerative potential [64, 65]; however, this interpretation is speculative and must be framed cautiously. In fact, excessive bleeding has been proposed as a potential indicator of preserved vascular/blood supply, which may contribute positively to pulp healing and reparative processes, provided that inflammation remains controllable. Recent translational data indicating that inflamed pulps retain viable stem/progenitor niches and robust angiogenic signaling provide biological plausibility [5, 66], yet definitive histological validation linking bleeding duration to healing outcomes is lacking. Thus, while bleeding observations can enrich intraoperative assessment, they should not dictate treatment escalation in isolation but instead be integrated into a broader clinical and biological framework. Thus, while bleeding duration provides useful biological insight into inflammatory severity, it should not be interpreted in isolation as a prognostic determinant; treatment decisions must always be contextualized within the overall clinical/radiographic presentation.

Finally, translational research points toward a new frontier in regenerative endodontics. Beyond the established roles of CSBs, emerging approaches such as exosome-mediated signaling, stem cell aggregates, and biomimetic scaffolds provide novel avenues to modulate inflammation, enhance pulp-dentin complex regeneration, and integrate immune, vascular, and neural repair. These innovations extend the concept of VPT from a biologically supported therapy to a platform for next-generation tissue engineering, linking inflammation/infection control and host modulation with regenerative design. Ultimately, while the accumulating evidence strongly supports a paradigm shift, standardization of protocols and alignment of diagnostic criteria with biological reality remain essential prerequisites for universal adoption.

Taken together, the accumulated clinical and biological evidence mandates a shift from extirpation-based management of IP toward preservation-centered strategies that harness pulpal healing capacity. VPTs, supported by guideline-level evidence and regenerative biomaterials, are increasingly recognized as the standard of care for managing teeth with vital, inflamed pulps. The redefinition of diagnostic categories, alignment of clinical protocols with biological reality, and integration of translational advances will collectively ensure that endodontics moves beyond the limits of symptom-based determinism into a new era of minimally invasive, biologically driven care.

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3. Conclusion

From a clinical standpoint, the accumulated evidence strongly supports VPT as a viable and often preferable first-line therapy for permanent teeth with vital, inflamed pulps, even when traditionally labeled as IP. RCT should be reserved for cases of confirmed pulp necrosis or failures of VPT. By preserving vitality, maintaining structural integrity, and reducing treatment burden, VPT not only aligns with biological reality but also represents one of the most patient-centered, minimally invasive, and cost-effective methods currently available in endodontics, though further refinement of diagnostic tools, long-term follow-up, and patient-reported outcomes are still needed. Future studies integrating molecular biomarkers with clinical criteria may finally reconcile diagnostic terminology with the true biological capacity of the pulp.

Transparency:

The author confirms that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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