Regenerative Endodontics: A Systematic Analysis of the Failed Cases

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Abstract

Introduction: The aim of this systematic review was to analyze failed cases of regenerative endodontic treatment (RET) reported in the literature in terms of etiology, diagnosis, treatment protocols, signs of failure, and additional endodontic interventions. **Methods:** Electronic searches were performed in PubMed, Web of Science, and ProQuest Dissertations & Theses databases. All *in vivo* publications in humans that reported at least 1 failed case of RET were included in this systematic review. Failed RET cases were defined in the current study as any case that required an additional endodontic intervention or extraction after the completion of the initial RET. **Results:** A total of 28 studies that reported 67 failed cases of RET were included in this review. A total of 37 failed RET cases reported the etiology that resulted in the initiation of RET; 59% of these cases were caused by dental trauma, and 30% were caused by dens evaginatus. A total of 26 (39%) failed RET cases were detected at least 2 years after the initiation of RET. A total of 53 (79%) failed RET cases were presented with signs and/or symptoms of persistent infection. **Conclusions:** Persistent infection was the main presentation in 79% of failed RET cases. Furthermore, 39% of failed RET cases were identified after more than 2 years of follow-up. Future studies should include a detailed description of the etiology, preoperative variables, intraoperative protocols, and postoperative follow-up to provide a better understanding of failed cases after RET. *(J Endod 2019;■:1–11)*

Key Words

Dental trauma, dens evaginatus, disinfection, endodontic regeneration

Significance

There is a need for a detailed description of the etiology, diagnosis, clinical protocols, and postoperative follow-up to provide a better understanding of the circumstances surrounding the failure or success of regenerative endodontic treatments.

Regenerative endodontics has been recommended as the treatment of choice in cases of immature teeth with necrotic pulps. The majority of clinical regenerative endodontic treatment (RET) cases reported in the literature have shown positive clinical outcomes (1, 2). The absence of clinical signs and symptoms and radiographic evidence of periapical healing have been recognized as the primary indications of a successful endodontic regeneration procedure (3). Additionally, increased thickness of the root walls and/or increases in the length of the immature root as well as regaining the vitality of the tooth have been identified as additional goals of RET and indicate a high level of success (3). On the other hand, there is no clear consensus in the literature to define the failure of RETs. The presence of signs and symptoms after RET has been identified as a clear presentation of failure in multiple RET cases (4–6). However, other presentations of failure reported in the literature may be controversial, such as the inability to introduce blood into the canal (7, 8), tooth discoloration (9), the absence of any increase in root length (10), tooth fracture (11), and coronal leakage (12).

Since the reintroduction of RET in its current form, the evidence-based clinical outcomes have been derived by case reports/series with favorable outcomes. Nevertheless, the major concern related to this level of evidence is that it may not accurately represent the true outcomes of RETs, taking into consideration that most of the cases with unfavorable outcomes are underreported. In the last 5 years, multiple prospective and retrospective clinical studies related to RET were introduced into the literature (1, 2, 13, 14). These types of studies provide a higher level of evidence related to successful outcomes of RET and offered a relatively better description of cases with failed RET. Managing cases with failed RET requires careful treatment planning and immediate intervention to address the multiple challenges in a timely manner. The major challenge is the presence of an already compromised tooth with a necrotic pulp and an open apex. The other challenges are represented by the development of additional complications that developed after an unsuccessful attempt of RET such as tooth discoloration and/or signs and symptoms of persistent apical infection. To date, a systematic review of the peer-reviewed literature focusing on the failed cases of RET has yet to be published. Thus, the aim of this systematic review was to analyze all failed cases of RET reported in the literature. This includes identifying the etiology for the initiation of RET in these cases, the initial diagnosis of failed cases, treatment

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0099-2399/$ - see front matter

https://doi.org/10.1016/j.joen.2019.02.004

protocols used in these cases, signs of failure, time of failure, and additional endodontic interventions used to manage such cases.

Materials and Methods

The authors performed an electronic search using the PubMed search engine in May 2018 to identify publications that reported RETs. The search strategy was based on a recently published systematic review of the literature with some modifications (15). The search strategy included a combination of various key words and Medical Subject Headings terms pertinent to RET (Appendix 1). All terms related to a mineral trioxide aggregate (MTA) apical plug that were used in the previous systematic review (15) were not used in the current study. Furthermore, the search was expanded by including the Web of Science and the ProQuest Dissertations & Theses databases using the search terms "pulp regeneration," pulp revascularization," and "regenerative endodontics."

All *in vivo* publications in humans with a systematized attempt to perform RET were initially selected and read in full by 2 authors including case reports, case series, comparative, prospective, and retrospective clinical studies. All publications that reported at least 1 failed case of RET were finally identified and included in this review. Because of the lack of consensus in the literature that defines failure outcome in RET, failed RET was defined in the current study as any case of RET that required an additional endodontic intervention or extraction after the completion of the initial RET.

Data extraction from all detected failed cases was performed using a standardized form that included the following information: author and year of the publication, type of publication, number of failed cases, age and sex of the patients with failed cases, type of tooth, etiology, diagnosis, protocol used in treating these cases (ie, irrigation, intracanal medicaments, and inclusion of any specific scaffold), number of visits needed to finish the treatment, time elapsed between finishing the initial RET and the reported failure, and additional endodontic treatment performed after failure.

Results

General Description of Included Studies

Figure 1 details the flow of the search strategy. A total of 1489 studies were initially identified. After removing the duplicates, screening the titles and the abstracts of the identified studies, and excluding all nonhuman studies, 205 articles were identified. Then, the clinical articles not related to RET as well as RET clinical articles that did not report any failed cases were excluded. A total of 28 studies that had at least 1 failed case of RET were identified, including 15 case report/series (5, 6, 9, 10, 16–26), 7 retrospective studies (4, 11, 12, 27–30), 5 prospective studies (7, 8, 13, 31, 32), and 1 randomized clinical trial (14) (Table 1).

The number of failed RET cases per study ranged from 1 to 15, and the total number of failed cases identified were 67. These 67 cases are as follows: 21 of the failed cases were obtained from case reports/case

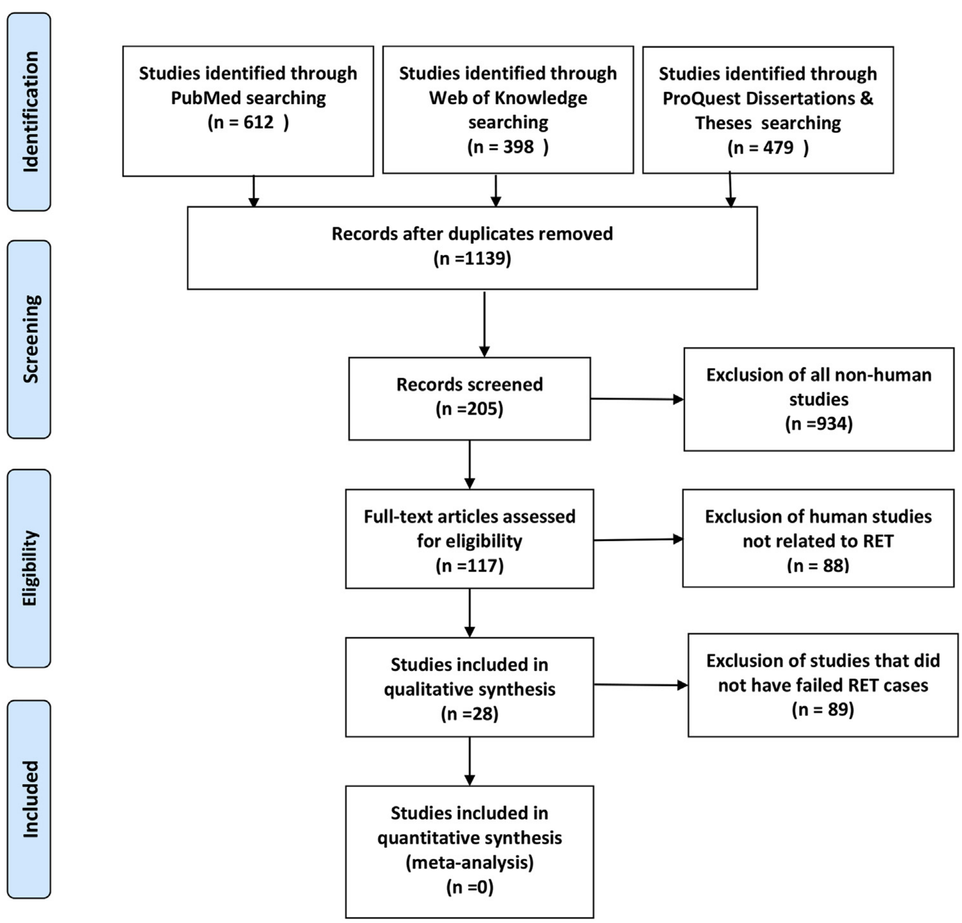

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search.

TABLE 1. Preoperative Factors and Etiology of Failed Regenerative Endodontic Treatment Cases Included in This Study

Study	Year	Type	Age (y)	Sex	Tooth	Etiology	Diagnosis
Ding (7)	2009	Prospective	8–11	Female	NA	NS	Acute or chronic apical periodontitis
				Female	NA	NS	Acute or chronic apical periodontitis
Torabinejad (16)	2012	Case report	11	Male	4	Iatrogenic mishap	Necrotic pulp with symptomatic apical periodontitis
Shimizu (18)	2012	Case report	10	Male	9	Trauma	Irreversible pulpitis with normal apical tissue
Nosrat (9)	2012	Case report	14	Female	8	Trauma	Necrotic pulp with symptomatic apical periodontitis
			14	Female	9	Trauma	Necrotic pulp with symptomatic apical periodontitis
Martin (19)	2013	Case report	9	Male	30	Caries	Necrotic pulp with symptomatic apical periodontitis
Shimizu (17)	2013	Case report	9	Male	9	Trauma	Necrotic pulp with chronic apical abscess
Nosrat (10)	2013	Case report	8	Male	8	Trauma	Necrotic pulp with acute apical abscess
McTigue (21)	2013	Case series	6	NS	24	Trauma	Necrotic pulp with chronic apical abscess
Alobaid (11)	2014	Retrospective	8.8 ± 1.6	NS	Anterior	Trauma	NS
			8.8 ± 1.6	NS	Anterior	Trauma	NS
			8.8 ± 1.6	NS	Anterior	Trauma	NS
			8.8 ± 1.6	NS	Anterior	Dens evaginatus	NS
Nagy (13)	2014	Prospective	10	Male	7	NS	NS
			12	Female	8	NS	NS
			9	Male	10	NS	NS
Lin (22)	2014	Case report	6	Male	9	Trauma	Previously initiated with asymptomatic apical periodontitis
Bezgin (8)	2015	Prospective	7	Male	9	Trauma	Necrotic pulp with or without apical pathosis
Khoshkhounejad (23)	2015	Case report	16	Male	9	Trauma	Necrotic pulp with asymptomatic apical periodontitis
Priya (20)	2016	Case report	11	Male	9	Trauma	NS
Bukhari (12)	2016	Retrospective	8-31	NS	8	Trauma	Necrotic pulp with or without apical pathosis
				NS	9	Trauma	Necrotic pulp with or without apical pathosis
				NS	Molar	Caries	Necrotic pulp with or without apical pathosis
Estefan (31)	2016	Prospective	18	Female	8	NS	Necrotic pulp with or without apical pathosis
			13	Male	10	NS	Necrotic pulp with or without apical pathosis
Chen (29)	2016	Retrospective	10.9 ± 0.98	NS	Premolar	Dens evaginatus	Necrotic pulp
Zizka (24)	2016	Case reports	8	Female	9	Trauma	Previously initiated with acute apical abscess
			8	Male	8	Trauma	Previously initiated with acute apical abscess
Chaniotis (6)	2017	Case reports	8	Male	9	Dens evaginatus	Necrotic pulp with asymptomatic apical periodontitis
			8	Male	9	Dens evaginatus	Necrotic pulp with chronic apical abscess
			7	Female	8	Trauma	Necrotic pulp with symptomatic apical periodontitis
Silujjai (4)	2017	Retrospective	11	NS	9	Trauma	Necrotic pulp with chronic apical abscess
			10	NS	20	Dens evaginatus	Necrotic pulp with chronic apical abscess
			13	NS	29	Dens evaginatus	Necrotic pulp with chronic apical abscess
			13	NS	20	Dens evaginatus	Necrotic pulp with chronic apical abscess
Al-Tammami (26)	2017	Case report	10	Female	8	Trauma	NS
Chatha (30)	2017	Retrospective	13	Male	Anterior	NS	Necrotic pulp with or without apical pathosis
Dhaimy (25)	2017	Case report	18	NS	31	NS	Necrotic pulp with chronic apical periodontitis

(*continued*)

TABLE 1. *(continued)*

Study	Year	Type	Age (y)	Sex	Tooth	Etiology	Diagnosis
Chan (32)	2017	Prospective	9.23 ± 2.36	NS	NA	NS	Necrotic pulp with or without apical pathosis
				NS	NA	NS	Necrotic pulp with or without apical pathosis
Botero (14)	2017	RCT	6–25	NS	NA	NS	Necrotic pulp
			6–25	NS	NA	NS	Necrotic pulp
			6–25	NS	NA	NS	Necrotic pulp
			6–25	NS	NA	NS	Necrotic pulp
Peng (27)	2017	Retrospective	10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
			10.8 ± 1.9	NS	NA	NS	Necrotic pulp with apical pathosis
Linsuwanont (28)	2017	Retrospective	11	NS	9	Trauma	Necrotic pulp with chronic apical abscess
			10	NS	20	Dens evaginatus	Necrotic pulp with chronic apical abscess
			13	NS	29	Dens evaginatus	Necrotic pulp with chronic apical abscess
			13	NS	20	Dens evaginatus	Necrotic pulp with chronic apical abscess
Lin (5)	2018	Case report	10	Male	10	Trauma	Necrotic pulp with apical periodontitis
			10	Male	20	Dens evaginatus	Necrotic pulp with apical periodontitis
			12	Male	13	Caries	Necrotic pulp with apical periodontitis

NA, not applicable; NS, not stated.

series, 32 of the failed cases were identified from retrospective studies, 10 cases were identified from prospective studies, and 4 cases were identified from randomized clinical trials.

Etiology and Diagnosis of Failed RET Cases

Among the failed cases that reported the sex of the patients, 19 cases occurred in males, and 9 occurred in females (Table 1). Sex was not specified in the other 39 cases. A total of 31 of failed RET cases occurred in anterior teeth, 10 in premolars, and only 3 in molars. The tooth type was not specified in the other 23 cases. A total of 30 failed cases did not report the etiology for the initiation of RET. On the other hand, 37 failed RET cases reported the etiology resulting in the initiation of RET. A total of 22 (59%) of these cases were caused by dental trauma, 11 (30%) were caused by dens evaginatus, and 3 (8%) by dental caries (Table 1). All failed cases that reported a pulpal diagnosis were either necrotic or previously initiated, except for 1 case (18) that reported irreversible pulpitis (Table 1). The majority of failed cases that reported periapical diagnosis had some form of apical pathosis. Only 1 case reported a normal apical area, 3 cases were diagnosed with acute apical abscess, 12 cases were diagnosed with chronic apical abscess, 2 cases were diagnosed with an acute or chronic apical periodontitis, 5 cases were diagnosed with symptomatic apical periodontitis, 3 cases were diagnosed with asymptomatic apical periodontitis, 18 cases reported a diagnosis of an apical periodontitis, and 23 cases did not report an apical diagnosis.

Disinfection Protocol Used in Failed RET Cases

A total of 66 (99%) failed cases reported the use of sodium hypochlorite (NaOCl) as the main irrigation solution with a concentration ranging from 1%–5.25% (Table 2). Furthermore, 7 cases (10%) used chlorhexidine (CHX) irrigation with a concentration ranging from 0.12%–0.2%. NaOCl was the only irrigation solution used in 33 (49%) of the failed cases, and 33 (49%) of the failed cases used various combinations of NaOCl, CHX, and EDTA. Only 1 failed case did not report the type of irrigation solution used. A total of 35 failed RET cases (52%) did not use EDTA in their irrigation protocols. Various combinations of an antibiotic intracanal medicament were used in 35 (52%) of the failed cases. $Ca(OH)_2$ was used in 9 (13%) cases, and 2 cases (3%) used both antibiotic combination and $Ca(OH)_2$ (Table 2). Additionally, 12 (18%) cases used an antibiotic combination or $Ca(OH)_2$ in their studies without specifically identifying the intracanal medicaments used in the failed cases. The type of intracanal medicament was not reported in 1 failed case, and 8 (12%) failed cases did not use intracanal medicament. A total of 58 (87%) cases were completed in multiple visits, whereas 8 (12%) cases were finished in 1 visit (Table 2). One failed case did not report the number of visits.

Scaffold Used in Failed RET Cases

A total of 61 (91%) failed cases used a blood clot as a scaffold. Three (4%) failed cases reported the use of platelet-rich plasma in the RET protocol, and 2 (3%) failed cases reported the use of an

TABLE 2. Intraoperative and Postoperative Factors of Failed Regenerative Endodontic Treatment Cases Included in This Study

Study	Causes of failure	Irrigation type	Type of medication	Number of visits	Capping material	Scaffold used	Time of failure	Alternative treatment
Ding (7)	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	NS	$Ca(OH)_2$ apexification
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	NS	$Ca(OH)_2$ apexification
Torabinejad (16)	Pain and sensitivity to cold	5.25% NaOCl	Antibiotic	Multiple	MTA	PRP	14 months	NSRCT
Shimizu (18)	Fracture	5.25% NaOCl	$Ca(OH)_2$	Multiple	MTA	Blood clot	3.5 weeks	Extraction
Nosrat (9)	Discoloration	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	6 years	NSRCT
	Discoloration and Caries	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	6 years	NSRCT
Martin (19)	Fracture	5.25% NaOCl	Antibiotic	Multiple	MTA	PRP	2 years 1 month	Extraction
Shimizu (17)	Fracture	2.60% NaOCl	$Ca(OH)_2$	Multiple	MTA	Blood clot	26 months	Extraction
Nosrat (10)	No increase in root length and discoloration	2.50% NaOCl	$Ca(OH)_2$ and next visit Augmentin paste	Multiple	MTA	Blood clot	31 months	MTA apexification
Mctigue (21)	Reinjured and the restoration was lost	3% NaOCl or 0.12% CHX	Antibiotic	Multiple	MTA	Blood clot	21 months	MTA apexification
Alobaid (11)	Signs and symptoms of infection	NaOCl, CHX, and/or EDTA	Antibiotic and/or $Ca(OH)_2$	Multiple	MTA	Blood clot	9 months	NSRCT
	Signs and symptoms of infection	NaOCl, CHX, and/or EDTA	Antibiotic and/or $Ca(OH)_2$	Multiple	MTA	Blood clot	8 months	NSRCT
	Signs and symptoms of infection	NaOCl, CHX, and/or EDTA	Antibiotic and/or $Ca(OH)_2$	Multiple	MTA	Blood clot	37 months	NSRCT
	Fracture	NaOCl, CHX, and/or EDTA	Antibiotic and/or $Ca(OH)_2$	Multiple	MTA	Blood clot	25 months	Extraction
Nagy (13)	Signs and symptoms of infection	2.6% NaOCl	Antibiotic	Multiple	MTA	FGF	2 months	MTA apexification
	Signs and symptoms of infection	2.6% NaOCl	Antibiotic	Multiple	MTA	FGF	3 months	MTA apexification
	Signs and symptoms of infection	2.6% NaOCl	Antibiotic	Multiple	MTA	Blood clot	6 months	MTA apexification
Lin (22)	Signs and symptoms of infection	5.25% NaOCl	$Ca(OH)_2$ and antibiotic	Multiple	MTA	Blood clot	16 months	Extraction
Bezgin (8)	Signs and symptoms of infection	2.5% NaOCl, 0.12% CHX, and 5% EDTA	Antibiotic	Multiple	MTA	Blood clot	8 months	NS
Khoshkhounejad (23)	Signs and symptoms of infection	5.25% NaOCl and 0.2% CHX	Antibiotic	Multiple	MTA	Blood clot	6 months	MTA apexification
Priya (20)	Internal and external resorption and signs and symptoms of infection	5.25% NaOCl	NS	Single	GIC	PRP	6 months	Second regeneration
Bukhari (12)	Coronal leakage	3% NaOCl and 17% EDTA	Antibiotic	Multiple	Bioceramic putty or MTA	Blood clot	22 months	MTA apexification
	Root resorption	3% NaOCl and 17% EDTA	Antibiotic	Multiple	Bioceramic Putty or MTA	Blood clot	1 month	NS

(*continued*)

TABLE 2. *(continued)*

Study	Causes of failure	Irrigation type	Type of medication	Number of visits	Capping material	Scaffold used	Time of failure	Alternative treatment
	NS	3% NaOCl and 17% EDTA	Antibiotic	Multiple	Bioceramic Putty or MTA	Blood clot	NS	NS
Estefan (31)	Signs and symptoms of infection	2.6% NaOCl and 17%EDTA	Antibiotic	Multiple	MTA	Blood clot	NS	MTA apexification
	Signs and symptoms of infection	2.6% NaOCl and 17%EDTA	Antibiotic	Multiple	MTA	Blood clot	NS	MTA apexification
Chen (29)	Signs and symptoms of infection	2.5% NaOCl	$Ca(OH)_2$	Multiple	MTA	Blood clot	NS	NS
Zizka (24)	Internal resorption and signs and symptoms of infection	1.5% NaOCl and 17% EDTA	$Ca(OH)_2$	Multiple	MTA	Blood clot	12 months	NSRCT
	Signs and symptoms of infection	1.5% NaOCl and 17% EDTA	$Ca(OH)_2$	Multiple	MTA	Blood clot	3 months	MTA apexification
Chaniotis (6)	Signs and symptoms of infection	3% NaOCl and 17% EDTA	NA	Single	MTA	Blood clot	4 years	MTA apexification
	Signs and symptoms of infection	3% NaOCl and 17% EDTA	NA	Single	Biodentine	Blood clot	12 months	NSRCT
	Signs and symptoms of infection	3% NaOCl and 17% EDTA	NA	Single	Biodentine	Blood clot	6 months	Second regeneration
Silujjai (4)	Signs and symptoms of infection	1.5%–2.5% NaOCl and 17% EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	20 months	NS
	Signs and symptoms of infection	1.5%–2.5% NaOCl and 17% EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	25 months	NS
	Signs and symptoms of infection	1.5%–2.5% NaOCl and 17% EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	37 months	NS
	Signs and symptoms of infection	1.5%–2.5% NaOCl and 17% EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	35 months	NS
Al-Tammami (26)	Signs and symptoms of infection	NS	NS	NS	MTA	NS	2 years	Second regeneration
Chatha (30)	Signs and symptoms of infection	1.5% NaoCl and 17% EDTA	$Ca(OH)_2$	Multiple	MTA	Blood clot	NS	NS
Dhaimy (25)	Signs and symptoms of infection	1 % NaOCl	Antibiotic	Multiple	MTA	Blood clot	10 months	MTA apexification
Chan (32)	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	NS	MTA apexification
	Financial	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	NS	Extraction
Botero (14)	Signs and symptoms of infection	2.5% NaOCl and 17% EDTA	NA	Single	MTA	Blood clot	3 months	MTA apexification
	Signs and symptoms of infection	2.5% NaOCl and 17% EDTA	NA	Single	MTA	Blood clot	3 months	MTA apexification
	Signs and symptoms of infection	2.5% NaOCl and 17% EDTA	NA	Single	MTA	Blood clot	3 months	MTA apexification
	Signs and symptoms of infection	2.5% NaOCl and 17% EDTA	NA	Single	MTA	Blood clot	12 months	MTA apexification
Peng (27)	Fracture	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	16 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	MTA	Blood clot	27 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	12–24 months	NS

	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	12–24 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	12–24 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	25–36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	>36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	>36 months	NS
	Signs and symptoms of infection	5.25% NaOCl	Antibiotic	Multiple	GIC	Blood clot	>36 months	NS
Linsuwanont (28)	Signs and symptoms of infection	NaOCl and EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	20 months	NS
	Signs and symptoms of infection	NaOCl and EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	96 months	NS
	Signs and symptoms of infection	NaOCl and EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	37 months	Extraction
	Signs and symptoms of infection	NaOCl and EDTA	Antibiotic or $Ca(OH)_2$	Multiple	MTA	Blood clot	35 months	Extraction
Lin (5)	Signs and symptoms of infection	3.25% NaOCl and 17% EDTA	$Ca(OH)_2$	Multiple	MTA	Blood clot	1year and 10months	NSRCT
	Signs and symptoms of infection	3.25% NaOCl and 17% EDTA	$Ca(OH)_2$	Multiple	MTA	Blood clot	1year	NSRCT
	Signs and symptoms of infection	3.25% NaOCl and 17% EDTA	$Ca(OH)_2$	Multiple	MTA	Blood clot	1year and 2months	NSRCT

$Ca(OH)_2$, calcium hydroxide; CHX, chlorhexidine; FGF, fibroblast growth factor; GIC, glass ionomer cement; MTA, mineral trioxide aggregate; NA, not applicable; NaOCl, sodium hypochlorite; NS, not stated; NSRCT, nonsurgical root canal therapy; PRP, platelet-rich plasma.

injectable scaffold impregnated with a basic fibroblast growth factor (Table 2). One failed RET case did not mention the type of scaffold used.

Signs for Failed RET Cases and Additional Endodontic Interventions

The reported time elapsed between the initiation of RET and the identification of the failed cases ranged from 3 weeks up to 8 years. Sixteen failed cases (24%) were detected less than 1 year after the initiation of RET, 16 failed cases (24%) were detected within 1–2 years of the initiation of RET, and 26 failed cases (39%) were detected at least 2 years after the initiation of RET (Table 2). Only 9 failed cases (13%) did not report the time of failure. Fifty-three failed cases (79%) presented with single or multiple signs and/or symptoms of persistent infection; fracture was reported as the main reason of failure in 5 cases (7%), tooth discoloration was reported as a reason of failure in 3 cases (5%), and coronal leakage was reported as the reason of failure in 2 cases (3%) (Table 2). The management of failed RET cases was reported in 41 cases (61%). The remaining 26 cases (39%) did not report the additional endodontic intervention used. The reported interventions included the use of MTA to fully fill the root canal or as an apical plug in 17 cases (25%), nonsurgical root canal treatment was used as the final treatment of choice in 11 cases (16%), extraction was performed in 8 cases (12%), a second RET was used in 3 cases (5%), and $Ca(OH)_2$ apexification was used in 2 cases (3%).

Discussion

The current study aimed to pool and analyze all failed cases of RET reported in the literature. This could help identify the complicated cases that are expected to pose some challenges during RET, recognize the limitations of the clinical protocols used to treat these cases, and highlight the need of better reporting modalities of failed RET cases. However, the main challenge of compiling all failed cases of RET is that different studies have used different criteria to identify failed cases. In the current study, we defined a failed RET as any case that required an additional endodontic intervention or extraction after the completion of the initial RET procedure. This definition of a failed RET enabled us to include RET cases that were deemed to be unsuccessful by various studies, regardless of the detailed criteria used to identify the RET failure in any specific study or case report. Nevertheless, some of the failed RET cases included in this study may not be acknowledged as unambiguous failed cases. For instance, RET was identified as failed in some cases because of discoloration and recurrent caries (9, 10), crown fracture (11, 17, 19), or loss of coronal restoration of the treated teeth (12, 21). All these scenarios may not be an accurate reflection of a failed RET but rather specific complications necessitating additional endodontic intervention.

Among the failed cases that reported the etiology for the initiation of RET, dental trauma compromised 59% of the cases followed by the presence of dens evaginatus (30%). A previously published review found that the etiology of 30% of all cases treated with RET was dental trauma followed by the presence of dens evaginatus (22%) (33). Dental trauma was suggested to cause root resorption (34) and may induce damage to the apical papilla and the Hertwig epithelial root sheath, which may lead to failure of the RET (2). Indeed, multiple failed cases of RET reported an etiology of a severe traumatic incident for the treated teeth such as avulsion (12, 20, 22) or luxation (5, 8). Nevertheless, most cases of failed RET with an etiology of dental trauma did not report the type of traumatic injury. A recent clinical study revealed that RET cases with an etiology of dens evaginatus had significantly better outcomes than RET cases with an etiology of dental trauma (2).

The vast majority of failed RET cases were diagnosed with necrotic pulp and some form of apical pathosis. The presence of established periapical pathosis in cases of a necrotic pulp with an immature apex may render the disinfection of these cases more challenging and less predictable. A previous review found that the history of pulp necrosis in 18 cases with successful treatment is no longer than 6 months (9). The same review also proposed a relationship between the duration of pulp necrosis and the outcome of RET (9). Our current study found that single or multiple signs and/or symptoms of persistent infection were the main presentation of RET failure in 79% of cases. A recent *in vivo* study showed the presence of a significant association between residual bacteria and the lack of periapical osseous healing (35). The same study also found a significant association between the presence of a periapical radiolucency and the lack of increased root wall thickness. Furthermore, the residual bacterial biofilms and their by-products have been found to modify the osteogenic differentiation of stem cells from apical papillae (36). Previous publications (2, 6, 22, 24, 35) indicate that maintaining a high level of disinfection during and after RET is important to improve the outcomes of RET. The use of high concentrations of irrigation solutions and antibiotic medicaments is the easiest way to improve the disinfection protocols during RET because NaOCl (37), CHX (38), and antibiotic intracanal medicaments (39) were found to have concentration-dependent antibacterial effects against biofilms formed by endodontic pathogens. However, the main disinfection dilemma in RET is that a lower concentration of various intracanal medicaments and irrigation solutions is recommended to maintain the survival of stem cells from apical papillae (40–43). Therefore, different disinfection approaches should be investigated in an attempt to deliver a lower concentration of antibacterial irrigations and medicaments that can maintain a higher level of disinfection and offer residual antibacterial effects. It is also worth noting that higher concentrations of antibiotic medicaments as well as $Ca(OH)_2$ can cause adverse effects on the mechanical (44), physical (45), and chemical properties (45, 46) of radicular dentin.

Tooth fracture was reported as the main reason of failure in 5 cases (11, 17–19, 27). The location of fracture in all 5 cases was reported to be in the cervical part of the crowns. However, none of the cases clearly reported whether there is radicular involvement of the fracture. The cervical third of the root is the area that is most susceptible to fracture in immature teeth (47). Furthermore, the use of antibiotic-based medicament or $Ca(OH)_2$ may negatively affect the fracture resistance in the cervical third of the roots (44).

Tooth discoloration was reported as the main reason of failure in 3 cases (9, 10). Discoloration after RET is an important patient-oriented outcome. However, the majority of RET studies do not acknowledge discoloration as a reason of failure (1, 21). Crown discoloration after RET is multifactorial in origin. It can be caused by the presence of minocycline in the antibiotic intracanal medicaments, the induction of bleeding during RET, and the application of MTA-based coronal barrier after RET (48). Various approaches have been suggested to minimize discoloration after RET. These approaches include the use of minocycline-free antibiotic medicament or $Ca(OH)_2$ (49), the application of intracanal medicament below the cementoenamel junction using an injectable syringe (43), sealing the pulp chamber with a dentin bonding agent (50), and the use of MTA alternatives for the coronal barrier such as Biodentine (51).

A nonintact coronal seal was reported in multiple failed cases of RET (12, 21). This could be a potential explanation for the initial resolution of periapical infection and root maturation before the reoccurrence of signs and symptoms of apical infection reported in some of the failed RET cases (6, 24, 27). The advantage of good coronal restoration for the long-term success of nonsurgical root canal treatment is well-documented (52). The effect of a coronal seal on the outcomes of RET is yet to be explored. However, the importance of a good coronal restoration after RET should not be underestimated.

In the current study, the time elapsed between the initiation of RET and the recognition of failed RET was more than 1 year in 63% of failed RET cases. Furthermore, 39% of all included failed RET cases were identified at least 2 years after the initiation of RET. Indeed, some of the failed RET cases reported evidence of initial favorable outcomes such as resolution of radiographic lesions (6, 24, 27), apical closure (5, 6), an increase in root length (4, 27), and an increase in root width (4, 24). This observation highlights the importance of long-term follow-up of RET before reporting any successful outcomes, specifically in randomized and prospective clinical studies. Multiple clinical studies of RET in the literature have reported a high success rate after a maximum follow-up period of 12–19 months (1, 2, 8, 13, 53). In a recent systematic review, the average follow-up time of RET studies was only 16.7 months (15).

In the current review, 8 failed RET cases were completed in a single visit without the use of intracanal medicaments (6, 14, 20). This approach may not be sufficient to provide an optimal disinfection protocol. However, previously published RET cases in the literature were performed in a single visit and reported to be successful (54–56). A current randomized clinical trial reported a 71% success rate of RETs after 2-visit RET and a 33% success rate after single-visit RET (14). However, the small sample size in that study was not enough to detect a statistical significant difference between the 2 groups (14).

Multiple cases of RET received additional endodontic treatment because of the inability to initiate bleeding within the root canal (7, 8, 14). These cases were not considered as failed RETs and were not included in this review as failed cases but rather as cases that were excluded before the completion of RET. The bleeding induction into the root canal during RET is a critical yet unpredictable step (9, 44). Indeed, multiple cases have reported difficulty to initiate bleeding even after the use of a vasoconstrictor-free anesthetic (9, 43, 45). Furthermore, some studies have shown radiographic evidence of continuing thickness of dentinal walls, apical closure, or increased root length despite the inability to induce bleeding into the root canal (43, 46), which suggests that the bleeding induction step may not be a clear predictor to determine the outcome of RET.

The majority of the failed RET cases that reported additional endodontic intervention were treated with an MTA apical plug. A recent comparative systematic review found that the pooled success rates for MTA apical plugs and RET were 94.6% and 91.3%, respectively (15). In cases of persistent infection after failed RET, a more intensive disinfection protocol can be used before proceeding to an additional endodontic intervention. Indeed, the current review identified 3 cases in which a second RET was attempted successfully after failed RET (6, 20, 26). On the other hand, there are multiple technical difficulties that make an additional disinfection protocol after a failed MTA apical plug challenging.

Despite the availability of continuously updated evidence-based clinical considerations from the American Association of Endodontists (43), there was a huge variability in the RET protocols used to treat cases reported in this review. This made any quantitative meta-analysis of these failed cases nonviable. The findings of this review should be viewed with caution because it only included failed RET cases without assessing the primary outcomes of the selected studies. Furthermore, there was missing essential information regarding the details of failed RET cases included in this review. This suggests the need for a detailed description of the etiology, diagnosis, clinical protocols, alternative interventions, and postoperative follow-up to provide a better understanding of the circumstances surrounding the failure or success of RET cases. Collectively, this systematic review showed that 63% of failed RET cases were identified after more than 1 year of follow-up. Persistent infection was the main presentation in 79% of failed RET cases. Additionally, MTA apexification was the endodontic treatment of choice in the majority of failed RETs that reported an additional endodontic intervention.

Acknowledgments

The authors deny any conflicts of interest related to this study.

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Appendix

Appedix 1. PubMed Search Strategy for Regenerative Endodontic Treatment

((((((((((((((((("Dental Pulp"[Mesh] AND "Necrosis"[Mesh]) OR "Dental Pulp Cavity"[Mesh]) OR "Dental Pulp Necrosis"[MeSH]) OR diseased pulp[tiab]) OR necrotic pulp[tiab]) OR necrotic pulps [tiab]) OR necrotic teeth[tiab]) OR necrotic tooth[tiab]) OR open apex[tiab]) OR open apices[tiab]) OR pulp gangrene[tiab]) OR pulp necrosis[tiab]) OR pulpal necrosis[tiab]) OR tissue necrosis [tiab]) OR traumatized pulp[tiab])) AND ((((((((("Dental Pulp" [Mesh] OR "Tooth"[MeSH]) OR "Tooth Apex"[MeSH]) OR "Tooth Root"[Mesh]) OR Immature apex[tiab]) OR Immature apices[tiab]) OR Immature permanent anterior teeth[tiab]) OR Immature permanent teeth[tiab]) OR Immature permanent tooth[tiab]) OR Immature teeth[tiab]) OR Immature tooth[tiab])) AND (((("Adolescent" [Mesh]) OR "Child"[Mesh])))) AND ((((((((((((("Mesenchymal Stem Cell Transplantation"[Mesh]) OR "Tissue Engineering"[Mesh]) OR "Root Canal Therapy"[Mesh]) OR dental pulp stem cells[tiab]) OR endodontic regeneration[tiab]) OR pulp regeneration[tiab]) OR pulp regeneration[tiab]) OR pulp revascularization[tiab]) OR pulp revitalization[tiab]) OR regenerative endodontics[tiab]) OR regenerative endodontic therapies[tiab]) OR tooth revascularization[tiab])) OR (((endodontics[tiab] AND regenerat*[tiab])) OR ("Endodontics" [Mesh] AND "Regeneration"[Mesh]))))