

EFFICACY OF ANTIBIOTICS AND STEROIDS AS INTRA-CANAL MEDICAMENT IN ENDODONTICS; A SYSTEMATIC REVIEW

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ABSTRACT

Endodontic infections are difficult and may cause long-term issues as well as accepted consequences. Cleaning the root canals is necessary to keep the tooth in a non-pathological state. Moreover, teeth that are growing and infected may delay the growth of the roots and eventually cause other issues. Anaerobic bacteria that are polymicrobial and required stand out in endodontic infections. Drugs like Ledermix may permeate the cementum and dentinal tubules to reach the periodontal and periapical tissues. Calcium hydroxide, dexamethasone, and triple antibiotic paste seem to help lessen surgical pain, especially in cases with symptomatic irreversible pulpitis. Using the PubMed, Medline, and ScienceDirect databases, a comprehensive evaluation of the literature from 2001 to 2022 was conducted. "Antibiotics, steroids, intracanal medication, and endodontic pain" were the keywords. After the screening procedure, nine studies were included, the majority of which indicated that endodontic pain is greatly affected by the combination of steroids and antibiotics. To investigate the relative efficacy of these drugs in more comprehensive clinical settings, additional investigation is necessary. All things considered, these investigations provide insightful information to the endodontic community, emphasizing the significance of customized intracanal drug selection for the best possible patient results.

Key words: Antibiotics, Steroids, Intracanal medicament, Endodontic pain.

Introduction

Endodontic infections are difficult and may cause long-term issues as well as accepted consequences. Cleaning the root canals is necessary to keep the tooth in a non-pathological state. Moreover, teeth that are growing and infected may delay the growth of the roots and eventually cause other issues. Anaerobic bacteria that are polymicrobial and required stand out in endodontic infections. Primary endodontic infections are mostly caused by *Prevotella* species, *Bacteroid melaninogenicus*, *Tannerella forsythia*, *Fusobacterium Nucleatum*, *Prophyromonas gingivalis*, *Prophyromonas endodontis*, *Spirochetes*, and a few other fungi and viruses. Persistent endodontic infections may result from some microorganisms that are resistant to disinfection techniques and can linger following endodontic treatment. When endodontic treatment fails, *Enterococcus faecalis* is consistently found in root canals. Due to its unique characteristics, this bacterium manages to survive in the root canal. Among these virulence factors include the ability to grow under conditions of malnutrition, the ability to survive and form biofilms in medicated canals, the ability to transition phenotypic into a viable but non-cultivable state, and the ability to use tissue fluids from the periodontal ligament and dentinal tubules [1]. A crucial phase in endodontic therapy is root canal disinfection, which entails getting rid of microbes from the root canal system [1].

The goal of disinfection is to reduce the amount of space that remains after the endodontic process and to establish an environment in the root canal system where germs cannot thrive. This is achieved through a mix of irrigation, mechanical instrumentation, intra-canal medication administration, and hermetic root canal obturation. Using rotary or manual endodontic files, mechanical instrumentation eliminates germs, debris, and damaged pulp tissue from the root canal system. About 50% of the root canal system remains uninstrumented due to the inability of these tools to reach the intricate architecture of the system, including fins, deltas, and ramifications. This means that endodontic irrigation must be used extensively in this area [2]. In addition to its bacteriocidal properties, an effective irrigant aids in the dissolution of organic detritus, the elimination of the smear layer, and the neutralization of endotoxins. Even with excellent chemo-mechanical preparation, remaining complex biofilms are difficult to break apart. After the canal system has been cleaned and shaped, pharmacological drugs called intracanal medicaments are inserted within the root canal and kept there for a while. These medications are specifically utilized in cases of necrotic pulp, acute symptoms in the canal draining, or a substantial periapical infection that is clinically or radiologically obvious. The medications stop inflammatory root resorption, lessen peri-radicular inflammation and discomfort, and eliminate any live bacteria

that may still be present in the radicular system. Additional reasons for the use of root canal medications include apexification and pulp revascularization. With positive outcomes, CH has been a great root canal medication in modern endodontic treatment [3, 4].

Both the patient and the endodontist are very concerned about pain before, during, and after endodontic treatment. To treat the symptoms, anti-inflammatory drugs need to be added to these intracanal medications. The main motivation behind Ledermix paste development was the use of corticosteroids to manage pulp and periapical disease-related pain and inflammation [5]. Medications like Ledermix (Lederle Pharmaceuticals, Wolfsrathshausen, Germany) may diffuse into the periodontal and periapical tissues by passing via the cementum and dentinal tubules. According to research by Abbott *et al.* the dentinal tubules serve as the main pathway for supplying the active ingredients to the periradicular tissues. On the other hand, a supply pathway was more important than the apical foramen. In root canal treatment, combination medications that have both corticosteroid and antibiotic components work quite well. The corticosteroid component provides almost immediate pain relief and decreases periapical inflammation. Additionally, it lessens periapical inflammation in patients who report experiencing severe discomfort with percussion after canal instrumentation. Antibiotics are designed to have antimicrobial characteristics [6].

Other products on the market serve the same function but promise even greater outcomes. Among such are medications that include EDTA (ethylene diamine tetraacetic

acid) and chlorhexidine. For the majority of endodontic infections, local antibiotic treatment is advised over systemic antibiotic therapy. The reasoning for this is that, particularly in cases when the pulp is necrotic, systemically delivered medications will not reach the radicular system, where the antibiotics will be effective at the appropriate concentrations. Additionally, the risk of adverse effects, allergies, antibiotic resistance, and inadequate patient compliance is eliminated with locally administered antibiotics [7].

Materials and Methods

Using the databases PubMed, Medline, and ScienceDirect, a comprehensive evaluation of the literature from 2001 to 2023 was conducted. The keywords used were “antibiotics, steroids, Intracanal medicament, and endodontic pain”. The method of selecting the articles that were searched for was shown in a PRISMA flowchart (**Figure 1**).

Inclusion criteria

- Case-control and randomized control studies.
- Published in English between 2001 and 2023.
- In vivo (humans).

Exclusion criteria

- Outside of the designated period.
- Language other than English.
- In vitro.
- systematic research, meta-analyses, opinions of specialists, or narrative reviews.

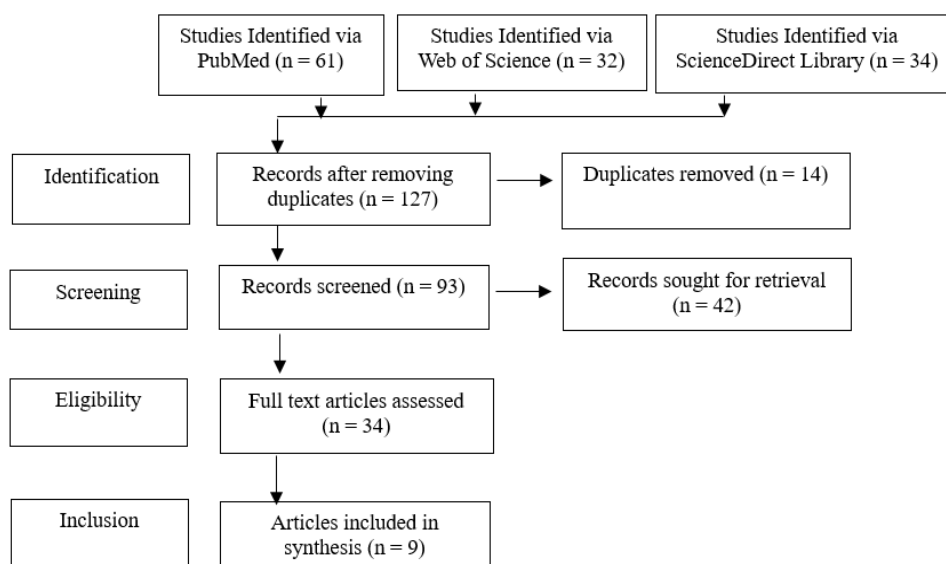


Figure 1. PRISMA Flow Diagram

Risk of bias assessment

Cochrane risk of bias assessment method was used to assess the quality of the studies included (**Table 1**).

Table 1. Summary of Cochrane Risk of Bias Assessment

Study	Selection Bias/ Appropriate control selection/baseline characteristics similarity	Selection bias in randomization	Selection bias in allocation concealment	Performance-related bias in blinding	Reporting bias/Selective reporting of outcomes	Detection bias Blinding outcome assessors	Accounting for confounding bias
Ali <i>et al.</i> (2020) [3]	+	-	+	+	+	+	+
Chu <i>et al.</i> (2006) [4]	+	+	+	+	+	+	+
Negm <i>et al.</i> (2001) [5]	+	+	+	+	+	+	+
Kundabala <i>et al.</i> (2006) [6]	+	+	-	+	+	-	+
Eftekhar <i>et al.</i> (2013) [7]	+	+	+	+	+	+	+
Gyanani <i>et al.</i> (2016) [8]	+	+	+	+	+	+	-
Tilakchand <i>et al.</i> (2020) [9]	+	+	-	+	+	+	-
Jindal <i>et al.</i> (2019) [10]	+	+	+	+	+	-	+
Dahake <i>et al.</i> (2020) [11]	+	-	+	+	+	+	+

Results and Discussion

In their study, Ali *et al.* (2020) [3] examined the frequency of postoperative endodontic pain brought on by intracanal drugs such as calcium hydroxide with dexamethasone vs triple antibiotic paste. a thorough investigation on the efficiency of steroids and antibiotics used intracranally in endodontic therapy. Group C had 17.5% of patients reporting pain-free after 72 hours, group B had 47.5%, and group A had 55%. Calcium hydroxide combined with dexamethasone and triple antibiotic paste helps reduce postoperative pain in teeth with symptomatic irreversible pulpitis; placebo showed no improvement (**Table 2**).

The purpose of Chu *et al.*'s experiment (2006) [4] was to determine how well a calcium hydroxide paste or an antibiotic/steroid drug would work for treating root canals with periapical radiolucencies. Before treatment, every channel—aside from one—exhibited cultivable growth. Following dressing with Ledermix, Septomixine, or Calasept, the corresponding percentages of canals with good development were 48% (13 of 27), 31% (8 of 26), and 31% (11 of 35).

In this randomized, double-blind study, Negm *et al.* (2001) [5] used vital pulp-test readings from 988 patients, 480 of whom also experienced pain during treatment, to assess the efficacy of a corticosteroid-antibiotic combination in treating posttreatment pain in teeth with endodontically affected teeth. Three visits were required to finish the endodontic operation. After taking the medication for 1, 2, 4, 8, 12, and 24 hours, ratings were completed. After being injected intracranally, the corticosteroid-antibiotic medication rapidly reduced the mean pain score (P.001). Up

until the study's end, it likewise considerably outperformed the placebo (P.001). Furthermore, there were no more incidents of pain, and there were no negative side effects from the drug.

The present clinical study by Kundabala *et al.* (2006) [6] sought to determine Ledermix paste's effectiveness as an intracanal treatment in teeth that were symptomatic by comparing it to eugenol as a control. Access cavities were made in thirty problematic teeth, and intracanal medicine was injected. We measured the frequency of pain and discomfort after access. Ledermix showed more rapid symptom reduction than eugenol did within 72 hours.

Eftekhar *et al.* (2013) [7] conducted a randomized control experiment where each of the three groups consisted of forty patients, and the twenty-one lower first and second mandibular molars with spontaneous soreness and percussion sensitivity were selected. Group 2 received a compound intracanal medicine, group 3 received a placebo, and Group 1's root canals were dressed with odontopaste. These groups' spontaneous pain and percussion sensitivity did not vary statistically significantly after seven days.

The goal of the Gyanani *et al.* research (2016) [8] was to evaluate the impact of two distinct single oral betamethasone pretreatment doses on the frequency of postoperative pain and inter-appointment flare-ups. Fifty-four endodontic patients, aged 18 to 59, were selected and split into three groups at random: either a placebo or betamethasone at two oral doses of 0.5 mg and 1 mg, respectively. Patients were given a questionnaire to complete and record their degree of discomfort at 1, 2, 3, and 7 days after therapy. The group that received 0.5 mg betamethasone had the lowest mean pain

ratings out of all the experimental groups; nonetheless, there was no statistically significant difference between the groups ($P > 0.05$).

The main goal of the Tilakchand *et al.* (2020) [9] investigation was to evaluate the antibacterial efficacy of a novel antibiotic-steroid paste against that of widely used (Ca(OH)₂), (DAP), and modified triple antibiotic paste (M-TAP). Eleven2 extracted human teeth had a 21-day *E. faecalis* infection. The canal was filled with Ca (OH) 2, DAP, M-TAP, a novel antibiotic-steroid paste, and a placebo. It was then sealed and incubated at 37°C in an aerobic setting.

The goal of this in vivo investigation by Jindal *et al.* (2019) [10] was to evaluate pain with different intracanal drugs. For this study, 75 permanent single-rooted mandibular premolars

with acute apical periodontitis were selected. Following access cavity preparation, cleaning, and canal shaping, patients were randomly assigned to five groups and intracanal administered a range of drugs, including calcium hydroxide paste, calcium hydroxide points, triple antibiotic paste, and Ledermix paste.

Dahake *et al.*'s study (2020) [11] sought to evaluate the antibacterial efficacy of three medications and their unique combination against certain endodontic infections. Using bacterial strains associated with the refractory endodontic condition, they conducted an in-vitro experiment to determine the MIC and MBC of Clindamycin (C), Metronidazole (M), and Doxycycline (D), as well as their combined CMD. All of the bacteria were severely inhibited by the CMD combination.

Table 2. Presents data on different studies, including their objectives, compared medications, postoperative pain incidence, antimicrobial effectiveness, and the impact of intracanal medication on pain.

Author's name	Study Objective	Medicament(s) Compared	Incidence of Postoperative Pain (%)	Antimicrobial Efficacy	Intracanal Medicament Effect on Pain
Ali <i>et al.</i> (2020) [3]	Efficacy of antibiotics and steroids as intracanal medicament in endodontics; a systematic review	Calcium hydroxide mixed with dexamethasone vs. Triple antibiotic paste vs. Placebo	Group A: 55%, Group B: 47.5%, Group C: 17.5%	-	Both calcium hydroxide combined with dexamethasone and triple antibiotic paste are effective in reducing postoperative pain in teeth with symptomatic irreversible pulpitis while Placebo showed little reduction in pain.
Chu <i>et al.</i> (2006) [4]	Comparison of antibiotics/steroid medicaments (Ledermix or Septomixine) vs. Calcium hydroxide paste (Calasept)	Ledermix vs. Septomixine vs. Calasept	Positive growth after treatment: Ledermix: 48%, Septomixine: 31%, Calasept: 31%	No significant differences in bacterial growth after treatment	No significant differences were observed between medicaments in terms of bacterial growth after treatment.
Negm <i>et al.</i> (2001) [5]	Corticosteroid-antibiotic combination vs. Placebo for posttreatment pain relief	Corticosteroid-antibiotic combination vs. Placebo	Medicament significantly reduced pain scores ($P < .001$) and was superior to Placebo throughout the study	No recurrences of pain and no side effects were noted	The corticosteroid-antibiotic combination was highly effective in reducing pain.
Kundabala <i>et al.</i> (2006) [6]	Ledermix paste vs. Eugenol as intracanal medicament	Ledermix vs. Eugenol	Ledermix showed faster action in reducing symptoms (within 72 hrs)	-	Ledermix was more effective in reducing symptoms compared to eugenol.
Eftekhar <i>et al.</i> (2013) [7]	Odontopaste® vs. Corticosteroid-containing compound vs. Placebo	Odontopaste® vs. Corticosteroid-containing compound vs. Placebo	No statistically significant differences in pain or percussion sensitivity after 7 days	-	No significant differences were observed between medicaments in pain or percussion sensitivity after 7 days.
Gyanani <i>et al.</i> (2016) [8]	Betamethasone (0.5 mg and 1 mg) vs. Placebo for inter-appointment flare-up	0.5 mg Betamethasone vs. 1 mg Betamethasone vs. Placebo	The 0.5 mg Betamethasone group had the lowest mean pain scores, but no significant differences between groups	-	No significant differences in pain between betamethasone groups and Placebo.

Tilakchand <i>et al.</i> (2020) [9]	Antimicrobial efficacy of antibiotic-steroid paste vs. Calcium hydroxide vs. Double antibiotic paste vs. Modified triple antibiotic paste vs. Placebo	Novel antibiotic-steroid paste vs. Ca (OH) ₂ vs. M-TAP vs. Placebo	Novel antibiotic-steroid paste showed similar antimicrobial properties as DAP	Novel antibiotic-steroid paste was comparable to DAP	Novel antibiotic-steroid paste had similar antimicrobial properties to DAP.
Jindal <i>et al.</i> (2019) [10]	Intracanal medicament effect on interappointment pain	Calcium hydroxide paste vs. Calcium hydroxide points vs. Triple antibiotic paste vs. Ledermix paste	Ledermix paste significantly reduced interappointment pain	-	Ledermix paste was highly effective in reducing interappointment pain compared to other medicaments.
Dahake <i>et al.</i> (2020) [11]	Assess the antibacterial effectiveness of medicines	Clindamycin (C), Metronidazole (M), Doxycycline (D), CMD combination	CMD combination suppressed all microorganisms, but: <i>E. Faecalis</i> , <i>B. Subtilis</i> , and <i>A. Actinomycetemcomitans</i> were substantially eliminated, while <i>C. Albicans</i> , <i>P. Aeruginosa</i> , <i>E. Coli</i> , and <i>S. mutans</i> showed resistance	. All of the bacteria were severely inhibited by the CMD combination.	

This systematic review of nine published articles provides valuable insights into using various intracanal medications and their impact on postoperative endodontic discomfort. The studies collectively suggest that the choice of intracanal medication plays a crucial role in managing posttreatment pain in endodontically affected teeth.

The level of pain experienced during and after a root canal treatment is often not a reliable indicator of how well endodontic therapy will work in the long run. To evaluate TAP and CH in combination with dexamethasone and placebo as intracanal analgesics for pain control after endodontic treatment [4]. A triple antibiotic paste that combines metronidazole, ciprofloxacin, and minocycline is very effective against gram-positive, gram-negative and anaerobic bacteria. According to one study, metronidazole inhibits *E. faecalis* more effectively than CH does, and TAP is even more potent as an intracanal anesthetic than CH. Following endodontic therapy, corticosteroids alleviate pain right away. Corticosteroids have long been used in dentistry in several ways. Intra-canal dexamethasone and ketorolac were shown to be more helpful in lowering postoperative pain than ibuprofen and placebo [12].

Genet *et al.*'s investigation on postoperative pain management found that endodontic discomfort usually subsides to a tolerable level in 3 days, which is in line with Kundabala *et al.*'s study [6]. Ledermix showed complete remission of symptoms, and eugenol reduced pain after 72 hours, indicating that intracanal drugs help with

postoperative symptoms. Intracanal medication is neither a panacea, a fix for insufficient debridement, or a substitute. Kaur's work on unpleasant teeth that have had endodontic treatment, which found a significant association between pre- and postoperative discomfort, is supported by the present research [13].

When combined with Ledermix or Odontopaste, calcium hydroxide does not seem to provide any advantages, according to Eftekhar *et al.* [7]. These combinations do not substantially increase antibacterial activity when compared to calcium hydroxide alone. Therefore, neither Odontopaste nor the other drugs used in this study were mixed with calcium hydroxide. There are disagreements over how much postoperative pain is influenced by age. Balban discovered that fewer acute aggravations of interappointment pain occurred as people aged. He cited the explanation that the pulp canal size dramatically reduces with aging. As a result, there would be less detritus, less blood flowing to the alveolus, and less inflammatory reaction to infection. Another investigation, a prospective randomized experiment by Kumar *et al.* found no connection between patient age and the frequency of interappointment discomfort, directly or indirectly. On the other hand, other investigations refute the notion presented above. Some experts say people over 50 are likelier to have flare-ups between appointments [14, 15].

Most of the actions mediated by glucocorticoids take time to manifest because gene expression and protein synthesis changes occur over time. The premedications were thus

administered to the individuals 30 minutes before the start of endodontic treatment. Although various organ systems may be affected by glucocorticoids, these effects are often only seen when supraphysiological dosages are administered over an extended period, typically over two weeks. According to the literature, even a hefty dosage of glucocorticoids has almost no adverse side effects [16].

One crucial discovery in a research [7] was that just one patient (Group A) had an emergency visit to treat clinical symptoms or a flare-up. Numerous experimental studies show that combining biopulpectomy with a placebo relieves pain in 71% of patients. The changed pulpal tissue's inflammatory mechanism is the primary cause of endodontic discomfort; as a result, pulpectomy, which involves removing the inflammatory tissue, may effectively relieve pain. Additionally, we cleaned and shaped the root canal using the crown-down approach. According to the literature, adopting the crown-down approach results in less periapical extrusion of debris and, thus, a lower incidence of postoperative pain [17].

The triple antibiotic paste used as an intracanal medication in the current investigation may have substantially decreased flare-ups. Metronidazole has a wide range of effects; it binds to DNA, damages the spiral helix, and hastens cell death. By attaching to the 30 S ribosome, the bacteriostatic drug minocycline prevents the production of proteins. DNA is harmed due to ciprofloxacin's inhibition of the bacterial DNA gyrase enzyme. Several studies have demonstrated that when propylene glycol and macrogol were employed as the vehicle as opposed to alternative delivery methods for the same medication, the penetration of the medication was higher. One crucial factor in this study was the choice of active pharmaceutical components to create the triple antibiotic paste. In contrast, if over-the-counter tablet medications are used, they may include numerous additional components (excipients) apart from the active substances, and the coating may prevent a homogeneous combination of the medications from forming [18].

Tilakchand *et al.* [9] created Ledermix paste to solve this flaw in the triple-antibiotic paste. The majority of its constituents are corticosteroid triamcinolone and tetracycline antibiotic demeclocycline. Triamcinolone's anti-inflammatory qualities contribute to patients' improved postoperative comfort. Demeclocycline is used due to its antimicrobial characteristics. Ledermix paste presents itself as a feasible treatment option for acute irreversible pulpitis once the inflammatory pulp has been extracted from the root canal system. Triamcinolone is used to treat the periradicular area that may have become irritated as a result of overuse of instruments. As a result, its direct effect on these tissues lessens inflammation. Additionally, demeclocycline has an antibacterial effect that combats microbes [19, 20].

In the study by Yousaf *et al.* Ledermix paste was shown to provide strong results in this investigation. They examined

the relationship between three drugs and postoperative discomfort in individuals who wanted to get well right away after a full biomechanical root canal debridement. They concluded that applying Ledermix paste—as opposed to calcium hydroxide, triple-antibiotic paste, or no dressing—to patients with sore teeth and acute apical periodontitis caused reduced discomfort [20-22].

When Ledermix paste was used as an intracanal medicine instead of calcium hydroxide, there was a substantial difference in the group's interappointment pain at a 48-hour interval, according to a study by Ghanbarzadegan *et al.* [17]. The results of this research support those of the other study.

In our study, the *E. faecalis* biofilm was destroyed by 1.5% NaOCl. This conclusion varies from prior studies that found robust antibiofilm effects of 1%–1.5% NaOCl without 100% biofilm eradication, but it also partially agrees with those earlier studies. This disparity may be due to the lower NaOCl exposure intervals (1-3 minutes) utilized in those studies compared to the 5-minute exposure times used in our inquiry, which is consistent with the therapeutic prescription of REPs [21, 23, 24].

The findings of our investigation demonstrated that a 5-min biofilm exposure to 2% CHX irrigants had an antibiofilm effect against 3-week-old *E. faecalis* but less effectively than the NaOCl group. According to recent *in vitro* studies, 2% CHX had a deleterious effect on the attachment and survival of stem cells from the apical and dental pulps. The antibacterial efficacy of several substances against a 3-week-old *E. faecalis* biofilm was evaluated in a study by Tilakchand *et al.* [9] who compared antibiotic-steroid paste, calcium hydroxide, DAP, M-TAP, and methylcellulose placebo paste. M-TAP, calcium hydroxide, antibiotic-steroid paste, and DAP showed the lowest levels of microbial inhibition, respectively, and the highest level [25].

To investigate the relative efficacy of these drugs in more comprehensive clinical settings, additional investigation is necessary. These investigations provide significant contributions to the field of endodontics by emphasizing the significance of customized intracanal drug selection for the best possible results for patients.

Conclusion

In summary, the use of Calcium hydroxide in conjunction with dexamethasone and triple antibiotic paste exhibits potential advantages in mitigating postoperative pain, particularly in cases with symptomatic irreversible pulpitis. Furthermore, the utilization of corticosteroid-antibiotic combos and Ledermix paste exhibits the potential to mitigate discomfort and sensitivity to percussion. Furthermore, the research indicates that the antibacterial effectiveness of certain medications, such as the CMD combination, can substantially eliminate specific bacterial strains linked to refractory endodontic conditions.

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