

Review Article

Antibiotics and Antibacterial Medications for Endodontic Treatments

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Abstract

Systemic and topical infections using irrigants are efficiently treated by antibiotics. Periapical lesions as well as microorganisms associated to the smear layer constitute the target of these therapies. In addition to dental and Peridontal infections, intracanal medicaments, such as ledermix, septomycine, tetracyclines, and the triple antibiotic paste including metronidazole, ciprofloxacin and minocycline, has been reported to be effective in the cleaning and bacterial inactivation of the root canal system. Topical antimicrobial and root canal irrigants may be used after the degradation of the dental pulp. These irrigants include calcium hydroxide, sodium hypochlorite and chlorhexidine. Others root medication such as EDTA, MTAD, triclosan, metronidazol, and phenol derivative are also efficient in this context. All these irrigants are functioning in close association with water, viscous or oil based vehicles. Root canal disinfection is a need before filling of root lumen with a stable paste and a tight seal of the coronal part of the tooth. Eliminating the bacterial smear layer constitute a crucial step which is a prerequisite leading to the regeneration of the radicular pulp, that plays a major role of restorative endodontic treatment allowing apexification.

Keywords

- Antibiotic
- Root canal irrigant
- Calcium hydroxide
- Sodium hypochlorite
- Chlorhexidine

INTRODUCTION

Antibiotics: Systemic infection, treatment of regional abscesses, and prescriptions to eradicate swelling

The aim of treatment of the root canal is to eliminate infection and exclude further re-infection of the canal. The essential role of root canal microbes in both primary and post-treatment apical periodontitis is now well-recognized. The major treatment procedure is the clinical management of problems associated with the control and elimination of infection [1].

The root canal flora of teeth with clinically intact crowns, but having necrotic pulps and diseased periapices, is dominated (> 90%) by anaerobes usually belonging to the genera *Fusobacterium*, *Porphyromonas* (formerly *Bacteroides*, *Prevotella* (formerly *Bacteroides*, *Eubacterium*, and *Peptostreptococcus*. *Spirochetes* and *fungi* are also present in necrotic infected root canals. The intraradicular survival and pathogenic properties of the endodontic flora are influenced by a combination of factors, including:

- a) Interactions with other micro-organisms in the root canal, to develop synergistically beneficial partners,
- b) The ability to interfere with host defense,
- c) The release of lipopolysaccharides (LPS) and other bacterial modulins,
- d) The synthesis of enzymes that damage host tissues.

LPS are historically known as endotoxins. They form an integral part of Gram-negative cell walls. They are released during disintegration of bacteria after death and during their multiplication. LPS interact with endothelial cells and macrophages. LPS not only signal the endothelial cells to express adhesion molecules but also activate macrophages to produce several molecular mediators such as the tumor necrosis factor- α (TNF- α) and interleukins. LPS are not the only bacterial degradation product that can induce mammalian cells to produce cytokines. Many proteins, certain carbohydrates, and lipids of bacterial origin are considered as belonging to a novel class of 'modulins' that induce the formation of cytokine networks and host tissue pathology.

Microbial collagenases, hyaluronidase, fibrinolysins, and several proteases are examples of enzymes produced by endodontic microorganisms. Microbes are also known to produce enzymes that degrade various plasma proteins.

Polymorphonuclear leukocytes (PMN), lymphocytes, plasma cells, and monocytes/ macrophages play role in the defense systems. The three major classes of lymphocytes are the T-lymphocytes, B-lymphocytes, and the natural killer (NK) cells. The T- and B-lymphocytes are substantial in apical periodontitis.

The thymus-derived (T) cells have been designated after their effects or function. For instance, the T-cells working with B-cells have been known as T-helper/inducer (Th/i) cells, and

those with direct toxic and suppressive effects on other cells have been named T-cytotoxic/suppressive (Tc/s) cells.

The B-lymphocytes directly responsible for antibody production are the bursa-equivalent (B) cells. Macrophages are phagocytic cells. Cytokines IL-1, TNF- α , interferons (IFN), and growth factors contribute to the release of prostaglandins and leukotrienes. Osteoclasts destroy bone and dental mineralized (dentinoclasts) tissues.

Interleukins (IL-1, -6, and -8), tumor necrosis factor- α (TNF) α , and IFN are χονσιδερεδ now ασ χψτοκινες. It is also the case for the colony-stimulating factors (CSF). Membrane lipids generate compound that are intra- and inter-cellular signals. Arachidonic acid, a 20-carbon polyunsaturated fatty acid, is released from membrane lipids and contributes to the formation of eicosanoids that mediate inflammatory response, Prostaglandins and leukotrienes are the two major groups of eicosanoids involved in inflammation.

The systemic antibiotic treatment

Antibiotherapy is requested to treat regional infection. Antibiotics are given for 7-10 days, combining drugs such as cephalosporins and ibuprofen, or tetracyclines with naproxen or diclofenac. They increase the bioavailability of the antibiotic. Microorganisms are the targets of antibiotic treatments.

The published data suggest the recommended clindamycin dose is 300 mg/6 hours, and 500 mg/8 hours, or 2000 mg/12 hours for amoxicillin-clavulanic acid. It was reported that the association spiramycin-metronidazole at the usual dosage fails to cover the full bacterial spectrum in infections taking origin from teeth disease. Amoxicillin-clavulanic acid, clindamycin and moxifloxacin are the antibiotics of choice for the treatment of odontogenic infections. A polymicrobial flora has been described in odontogenic infections, with strict anaerobes, and a relatively limited microbial spectrum. This means that a few drugs will suffice to treat odontogenic infections despite the empirical approach to management.

The use of antibiotics as prophylaxis for focal infection is usual in dental practice, and has been widely accepted in the dental profession. The paradigm of this model of treatment is the prevention of bacterial endocarditis, indicated patients at risk in the context of invasive procedures within the oral cavity [2].

Penicillin VK, 500mg, 4 times a day is the first choice antibiotic prescribed. Cindamycin 150mg, 4 time a day. Clindamycin and erythromycin were also prescribed together during a systematic exposure, the average duration being 6.80 to 7.58 days. Amoxicillin 500mg is the most prescribed, followed by the association amoxicillin/clavulanic acid. Metronidazole/spiramycin and clindamycin were also prescribed. Azithromycin and others were also recommended, but at very low doses.

Antibiotics as intracanal medicaments: topical action

Antibiotics have also been used as intracanal medicament. A triple antibiotic paste consisting of metronidazole, ciprofloxacin, and minocycline was shown to be effective against the pathogens commonly found inside the root canal system [3,4]. Calcium

hydroxide is effective as an intracanal medicament [5], however regenerative endodontic treatment with the triple antibiotic paste produced significantly greater increases in dentin wall thickness compared with Ca(OH)₂, MTA and nonsurgical root canal treatments (NSRCT) were the control groups. Regenerative endodontic treatment with the triple antibiotic paste and / or Ca(OH)₂ produced significantly greater increases in root length. Compared with the MTA apexification, control group with Ca(OH)₂ or formocresol resulted in significantly greater change in dentinal wall thickness. No difference was observed between these medicaments and the MTA apexification group. Whilst, systemic antibiotics appear to be clinically effective as an adjunct in certain surgical and nonsurgical endodontic procedures, their administration is not without the potential risk of adverse systemic effects, such as allergic reactions, cytotoxicity and the development of resistant strains of microbes.

Antibiotics used for root canal therapies: A series of antibiotics used as topical agents is listed in this part of the review (Table 1).

Ledermix is a glucocorticosteroid-antibiotic compound. The primary interest in developing Ledermix paste was based on the use of corticosteroids to control pain and inflammation associated with pulp and periapical diseases. Ledermix paste remains a combination of the same tetracycline antibiotic, demeclocycline-HCl (at a concentration of 3.2%), and a corticosteroid, triamcinolone acetonide (concentration 1%), in a polyethylene glycol base.

Septomixine Forte contains two antibiotics, neomycin and polymyxin B sulphate. Neomycin is bactericidal against Gram-negative bacilli but it is ineffective against *Bacteroides* and the related species, as well as against fungi. Polymyxin B sulphate is ineffective against Gram-positive bacteria, A routine 1-week application of Septomixine Forte was not effective in inhibiting residual intracanal bacterial growth between appointments. In addition, although the anti-inflammatory (corticosteroid) agent, dexamethasone is clinically effective, triamcinolone is considered to have less systemic side effects.

Tetracyclines: Tetracyclines including tetracycline-HCl, minocycline, demeclocycline and doxycycline are antibiotics with a broad spectrum that are effective against a wide range of microorganisms. They inhibit mammalian collagenases and clastic cells, and consequently have an anti-resorptive activity. The orifices of dentinal tubules are enlarged. They remove the smear layer. Tetracyclines bound into dentin are released without losing their anti-bacterial activity [6]. Tetracyclines are bacteriostatic in nature. This property may be advantageous because, in the absence of bacterial cell lysis, antigenic by-products such as endotoxins are not released. Tetracyclines also have many additional properties such as the inhibition of mammalian collagenases, that prevent tissue breakdown.

Triple antibiotic paste: Following the standard root canal treatment protocol and apexification, two antibiotics (metronidazole and ciprofloxacin) were placed in the canal, after which the canal was left empty. Radiographic examination showed the beginning of apical closure 5 months after the completion of the antimicrobial protocol. Thickening of the root

Table 1: Intracanal Medications and antimicrobial irrigants.	
1	INTRACANALAR ANTIBACTERIAL MEDICATION (1)
2	Ledermix – glucocorticosteroid – control pain & inflammation (2-4)
3	Streptomixine forte : neomycin & polymixine B Sulphate
	Tetracyclines : tetracycline-HCL, minocycline demeclocycline, & doxycycline- inhibition of mammalian collagenases (5, 6)
5	Triple antibiotic paste : metronidazole ciprofloxacin and minocycline (7,8). Prior to pulp regeneration.
6	ANTIMICROBIAL AND ROOT CANAL IRRIGANTS
7	Calcium hydroxide is a strong alkaline substance, dissociated into calcium and hydroxyl ions: Biocompatibility, encourage periapical hard tissue healing & inhibition of root resorption, and stimulation of periapical healing (9-13)
8	Sodium hypochlorite (NaOCl) is an oxidizing and hydrolyzing agent, bactericidal and proteolytic (14-16)
9	Chlorhexidine (CHX) potent antimicrobial agent, inhibiting metalloproteinase (17-18) CHX is effective in the control of dental plaque, in the prevention and treatment of caries. Its structural formula CHX consists of two symmetric 4-chlorophenyl rings and two biguanide groups connected by a central hexamethylene chain. The bactericidal effect of the drug is due to the cationic molecule binding to extra microbial complexes and negatively charged microbial cell walls. CHX is bactericidal and effective against Gram-positive, Gram-negative, facultative and strict anaerobes, yeasts and fungi, particularly <i>Candida albicans</i> . It is active against some viruses and inactive against bacterial spores at room temperature. CHX does not interfere with the collagen present in the organic matrix of root dentin and inhibits MMPs. Two % CHX containing medicaments is able to diffuse into the dentin and reach the outer surface, exerting antimicrobial action. CHX can be used during all phases of the root canal preparation, including the disinfection of the operative field, during the enlargement of the canals orifices and removal of necrotic tissues before root canal length determination in the chemo-mechanical preparation: alternating its use with an irrigation with an inert solution prior to the foraminal enlargement: as intracanal medicament alone or: combined with other substances. No adverse effects have been published regarding CHX use as an irrigant or intracanal medicaments. CHX adverse effects are usually related to its topical or oral application, including reversible discoloration of the tongue, teeth, and silicate or composite restorations, transient taste disturbances and a burning sensation of the tongue.
10	Ethylenediamine tetracetic acid (EDTA) . Seventeen % EDTA for 3 min removes the smear layer from the root canal walls. EDTA extracts bacterial surface proteins leading bacterial death.
11	Biopure™ MTAD (a Mixture of Tetracyclin, Acid and Detergent) is an endodontic irrigant, including a mixture of doxycycline, citric acid, and a detergent (Tween 80). It removes efficiently the smear layer.
12	Tetra clean eliminates the smear layer in dentinal tubules. It causes a high degree of biofilm disaggregation at each time interval when compared with MTAD.
13	Clindamycin is also an antimicrobial detergent, effective against many endodontic pathogens.
14	Phenol and phenol-derivatives used as an interappointment intracanal medicament.
15	Triclosan and Gantrez®, Metronidazole, Ozonated water, and Iodine compounds have been also efficiently used as root canal irrigants.

dentin and complete apical closure was confirmed 30 months after the treatment, indicating the revascularization potential of a young permanent tooth pulp in a bacteria-free root canal space.

To conclude with the intracanal antibacterial treatment:

1. The local application of antibiotics within the root canal system may be a more effective mode for delivering such drugs than systemic routes of administration.
2. Tetracyclines have been used to remove the smear layer from instrumented root canal walls, and for the irrigation of apical root-end cavities during periapical surgical procedures, and as an intracanal medicament.
3. Substantivity of tetracyclines has been shown for up to at least 12 weeks.
4. Ledermix, a glucocorticosteroid-antibiotic compound, has anti-inflammatory, anti-bacterial and antiresorptive properties, all of which help to reduce the periapical inflammatory reaction including clastic-cell mediated resorption.
5. A triple antibiotic paste consisting of metronidazole, ciprofloxacin and minocycline, has been reported to be very effective in the disinfection of the root canal system [7,8].

Antimicrobial and root canal irrigants

(Table 1) The treatment of endodontic infection is related to the topical control of the smear layer containing bacteria and their by-products. It prevents the penetration of intracanal medicaments into dentinal tubules and influences the adaptation of filling materials to the canal walls. Current methods of smear layer removal include chemical and physical techniques [9]. It was shown that the smear layer was made of particles ranging in size from less than 0.5-15 µm. It contains also remnants of odontoblastic processes, pulp tissue and bacteria. The thickness of the smear layer is about 1µm. Within the tubules, smear layer was found up to a depth of 40µm. Hydrodynamic disinfection was also carried out.

- 1) The thickness and volume of the smear layer is unpredictable. It is a good substrate for bacteria,
- 2) It may limit the penetration of disinfecting agents, acting as a barrier between the filling material and the canal wall,
- 3) It is a loosely adherent structure and potential avenue for leakage and bacterial contaminant passage.

Methods have been proposed to remove the smear layer. They include chemical removal [chlorhexidine, sodium hypochlorite, chelating agents, organic acid (such as citric acid, and to a lesser

degree, polyacrylic acid, lactic acid and phosphoric acid, tannic acid] (Table 1).

Bacteria can exist within the root canal itself, or within other regions such as the dentinal tubules, accessory canals, canal ramifications, apical deltas, and transverse anastomoses. Apart from the canal itself, all the other areas are inaccessible to mechanical instrumentation procedures, as well as the irrigating solutions used during endodontic treatment. In order to predictably eliminate as many bacteria as possible from the entire root canal system, a combination of mechanical instrumentation and irrigating solutions was used to remove or dissolve organic and inorganic debris, to destroy bacteria, to remove the smear layer and maintain dentine permeability [9,10].

Calcium hydroxide has been introduced by Hermann [11] and is a pulp capping agent.

The bacterial cytoplasmic membrane possesses important functions allowing the survival of the cells, such as

- (i) selective permeability and transport of solutes,
- (ii) electron transport and oxidative phosphorylation in aerobic species,
- (iii) excretion of hydrolytic exoenzymes,
- (iv) bearing enzymes and carrier molecules that function in the biosynthesis of DNA, cell wall polymers, and membrane lipids,
- (v) bearing the receptors and other proteins of the chemotactic and other sensory transduction systems [12] (Table 2).

Phospholipids and structural components of the cellular membrane are destroyed by $\text{Ca}(\text{OH})_2$. The bacterial DNA is splitted, and lethal mutations are induced. The effects on disinfection of root canals were observed only when the substance was in direct contact with bacteria in solution. In such conditions, the concentration of hydroxyl ions is very high, reaching incompatible levels to bacterial survival. Bacteria inside dentinal tubules may constitute an important reservoir and root canal infection or reinfection may occur during and after endodontic treatment. It stimulates hard tissue formation, the mineralized bridge being termed osteodentin. This barrier gives rise to the formation of bridges with the so-called tunnel defects.

Such defects favor bacterial re-infection.

Apically, the pH of the inner dentin reached a plateau of approximately 9.5 after 2 weeks. In the outer dentin, although the pH began to rise earlier, the maximum pH level was low, reaching just under 9 at 2 weeks. The pH of the cervical inner dentin peaked at 10.8 after 24 hours and settled to a stable pH value of just above 10. These results revealed that a dressing for 1 week with calcium hydroxide raised the pH of the inner dentin to approximately 9.0. Bacteria colonizing necrotic tissue in ramifications, isthmus, and irregularities are also protected from the action of calcium hydroxide, due to pH neutralization. Therefore, a short-term dressing with calcium hydroxide appears to eliminate mainly bacterial cells in direct contact with this substance, such as bacteria located in the main root canal or in the circumpulpal dentin. Theoretically, long-term use of calcium hydroxide may be necessary to obtain a bacteria-free root canal system. Bacteria may survive after intracanal medication for several reasons :

- First, infection dues from bacterial strains may be intrinsically resistant to the medicament.
- Secondly, bacterial cells may be enclosed within anatomical variations inaccessible to the medicament.
- Thirdly, medicaments may remain in the root canal system for insufficient time to reach and kill bacterial cells.
- Finally, bacteria may alter their pattern of gene expression after changes in the environmental conditions.

The influence of the vehicle on antimicrobial activity has to be taken into account. Most of the substances used as a vehicle for calcium hydroxide do not have significant antibacterial activities [13,14].

The ability of a medicament to dissolve and diffuse in the root canal system would seem essential for its successful action. Nevertheless, this substance owes its biocompatibility to its low water solubility and diffusibility. Cytotoxicity is limited to the tissue area in direct contact with calcium hydroxide. On the other hand, the low solubility and diffusibility of calcium hydroxide may make it difficult to reach a rapid and significant increase in the pH to eliminate bacteria within dentinal tubules [13,15].

Table 2: The lethal effects of calcium hydroxide on root canal bacteria are due to several mechanisms, namely.

1	(a) A chemical action through:
	1. Damage to the microbial cytoplasmic membrane by the direct action of hydroxyl ions,
	2. Suppression of enzyme activity and disruption of cellular metabolism,
	3. Inhibition of DNA replication by splitting DNA,
2	(b) Physically by:
	1. Acting as a physical barrier that fills the space within the canal and prevents the ingress of bacteria into the root canal system, and
	2. Killing the remaining micro-organisms by Wit holding substrates for growth and limiting space for multiplication.
3	(c) The biological properties of calcium hydroxide include:
	1. Biocompatibility (due to its low solubility in water and limited diffusion),
	2. The ability to encourage periapical hard tissue healing around teeth with infected canals, and
	3. Inhibition of root resorption and stimulation of periapical healing after trauma.

Table 3: The requirements for root canal irrigants. They need to

Have a broad antimicrobial spectrum and high efficacy against anaerobic and facultative microorganisms organized in biofilms,
(ii) Dissolve necrotic pulp tissue remnants,
(iii) Inactivate endotoxins,
(iv) Prevent the formation of a smear layer during instrumentation or dissolve the latter once it has formed,
(v) Be systemically nontoxic,
(vi) Be non caustic to periodontal tissues,
(vii) Be little potential to cause an anaphylactic reaction

Table 4 : The main advantages of CHX are.

a) Higher antimicrobial than that of CH alone,
b) A pH around 13, which is greater than that of CHX alone (pH 5.5-7.0) and could help in the control of the inflammatory internal- and external- root resorption,
c) Substantivity due to the presence of CHX,
d) Physical and chemical barrier better than that of 2% CHX gel, preventing root canal re-infection and interrupting the nutrient supply to the remaining bacteria,
e) The contact angle of CH combined with CHX is lower than that observed when CH is combined with water, increasing the wettability of the medicament, which may explain the increase in the antimicrobial activity of its association with CHX,
f) CHX improves CH properties of reducing the endotoxin content in root canals in vitro
g) Diffusion through the dentinal tubules.

Calcium hydroxide has a limited antibacterial spectrum that does not affect all members of the endodontic microbiota. Studies on the antimicrobial effect of $\text{Ca}(\text{OH})_2$ differed depending to the methodology, culture medium, and the bacterial strains used. The studies showed varied, even conflicting, results. $\text{Ca}(\text{OH})_2$ has a wide range of antimicrobial effects against common endodontic pathogens, but it is less effective against specific species such as *E. faecalis* or *C. albicans* [15]. It is implicated in pulp revascularization.

Antimicrobial solutions as root canal irrigants

Topical effects : The most widely used endodontic irrigant is 0.5% to 6.0% sodium hypochlorite (NaOCl), because of its bactericidal activity and ability to dissolve vital and necrotic organic tissue. However, NaOCl solutions don't exert any effects on the inorganic components of the smear layer. Chelant and acid solutions have been recommended for removing the smear layer from instrumented root canals, including ethylene diamine tetraacetic acid (EDTA), citric acid, and phosphoric acid [16].

Sodium hypochlorite: Sodium hypochlorite (NaOCl) is both an oxidizing and hydrolyzing agent. It is bactericidal and proteolytic. Sodium hypochlorite solutions have been used as a wound and an endodontic irrigant. As an endodontic irrigant, sodium hypochlorite solution is relatively cheap, bactericidal, and virucidal. It dissolves proteins, has a low viscosity, and a reasonable shelf life.

Commercial sodium hypochlorite solutions are strongly alkaline, hypertonic, and typically have concentrations of 10 to 14 per cent available chlorine. Excess chlorine in sodium hypochlorite solutions leads to an acid solution which is unstable. Concentrations over about 5 per cent available chlorine require containers to prevent build up of the oxygen produced.

The endodontic use of hypochlorite requires the removal of

dentin debris, the destruction of microorganisms and dissolution of proteins. Sodium hypochlorite solutions are effective endodontic irrigants over a wide range of concentrations. It is mandatory to store these solutions in opaque glass or coated polyethylene containers tightly sealed.

Irrigation of the infected root canal with 1%, 2.5%, and a 5.25% sodium hypochlorite (NaOCl) solution significantly reduce the number of bacterial cells. Irrigants are used during endodontic treatment to flush out loose debris, lubricate the dentinal walls, dissolve organic matter in the canal, and be antimicrobial. Cleaning and disinfecting procedures are highly dependent on the mechanical and chemical effects of the irrigants [14,16]. With 1% solution of NaOCl, the mean reduction of bacteria was 97.1%. Instrumentation and irrigation with 2.5% NaOCl provided a decrease of 99.9%. With a 5.25% concentration, the reduction was 99.8.

Chlorhexidine (CHX): A 2% chlorhexidine solution is a potent antimicrobial agent. CHX has been used in endodontics as an irrigating substance or intracanal medicament, as it possesses a wide range of antimicrobial activity, substantivity, lower cytotoxicity than NaOCl whilst demonstrating efficient clinical performance, lubricating properties, rheological action. It inhibits metalloproteinases. It is chemically stable, does not stain cloths. It is odorless, and water soluble. CHX has been recommended as an alternative to NaOCl, especially in cases of open apex, root resorption, foramen enlargement and root perforation, due to its biocompatibility, or in cases of allergy related to bleaching solutions.

Chlorhexidine is a synthetic cationic biguanide whose optimal antimicrobial activity is achieved within a pH range of 5.5–7.0. It binds to hydroxyapatite, creating a bacteriostatic milieu in the root canal. Chlorhexidine is a cationic molecule, which can be used during treatment. It has a wide range of antimicrobial

activity. Its cationic structure provides a unique property named substantivity [17].

CHX enters into the cell through some type of active or passive transport mechanism. CHX increases the permeability of the cell wall, which allows the CHX molecule to penetrate into the bacteria. CHX is a base and stable as a salt. At low concentration (0.2%), low molecular weight substances leak out of the cell. At higher concentration (2%), CHX is bactericidal and precipitation of the cytoplasmic contents occurs, which results in cell death. The 1% NaOCl and MTAD disrupt the biofilm, but did not eliminate bacteria. Chlorhexidine as well as tetracyclines have a unique feature in that dentin intermingle with it, and acquires antimicrobial substantivity. The positively charged ions are adsorb on dentin and prevent microbial colonization on the dentin surface. Antimicrobial substantivity depends on the number of CHX molecules available to interact with the dentin. A 2% chlorhexidine gel may be a more effective as intracanal medicament than calcium hydroxide paste against *Candida albicans* and *Enterococcus faecalis*.

CHX disrupts the cell membrane of both crevicular and peripheral blood neutrophils at concentrations above 0.005% within 5 min, indicating that its inhibitory effect on neutrophil function is mostly due to its lytic properties. Taken together, for the clinically used concentrations, the biocompatibility of CHX is acceptable. It may be concluded that CHX has a wide range of activity against both Gram positive and Gram negative bacteria. CHX has antibacterial substantivity and biocompatibility on dentin for up to 12 weeks [7].

CHX can be applied clinically as an antimicrobial agent during all phases of the root canal preparation. CHX is currently considered to be the gold standard of oral antiseptics and CHX is the most extensively researched preventive agent in dentistry.

For endodontic purposes, CHX can be used in a liquid or in a gel presentation. CHX gel consists of a gel base in a optimal pH range of 5.5 to 7.0. Using the agar diffusion test, 2% CHX gel was superior to 2% CHX liquid. At low concentrations, low molecular weight substances will leak out resulting in a bacteriostatic effect. At higher concentrations, CHX has a bactericidal effect due to precipitation of the cytoplasm of bacterial cells, resulting in cell death. The effectiveness of CHX stems from its capacity to adsorb to negatively charged surfaces therefore maintaining prolonged antimicrobial activity for several hours. Regarding its substantivity, it has been found that the use of CHX prevented microbial activity from 48 h up to 12 weeks.

Matrix metalloproteinases (MMPs) are members of a zinc ion enzyme family that require a zinc ion in their active site for catalytic activity. MMPs are active at neutral pH and can therefore catalyze the normal turnover of extracellular matrix (ECM) macromolecules such as the interstitial and basement membrane collagens, proteoglycans (aggrecan, decorin, biglycan, fibromodulin and versican), as well as ECM proteins such as fibronectin.

CHX has been used in endodontics and proposed as both an irrigant and an intracanal medicament. One of the mechanisms that can explain its efficacy is based on the interaction between

the positive charge of the molecule and the negatively charged phosphate groups on the bacterial cell wall, which allows the CHX molecule to penetrate into the bacteria with toxic effects. Therefore, its antimicrobial activity is not related to its pH (between 5.5 to 7) (Table 4) [17-18].

CHX affected cell viability in a dose and time-dependent manners. Its toxic effect consisted in the induction of apoptotic and autophagic/necrotic cell deaths and involved disturbance of mitochondrial function, intracellular Ca^{2+} increase and oxidative stress (Table 1).

Ethylenediamine tetraacetic acid (EDTA): EDTA with ultrasonics was efficient to remove the smear layer or debris from the apical region of the root canal, and/or to open the dentinal tubules. On direct exposure for extended time, EDTA extracts bacterial surface proteins by combining with metal ions from the cell envelope, which can eventually lead to bacterial death. In addition to EDTA, citric acid can also be used for irrigation of the root canal to remove the smear layer.

MTAD: MTAD is a mixture of 3% doxycycline, 4.25% citric acid, and Tween-80, as detergent. MTAD is a biocompatible material. It removes the smear layer, thus allowing doxycycline to penetrate the dentinal tubules and exert an antimicrobial effect. In the apical third, canals irrigated with MTAD (final irrigation) were cleaner compared with final irrigation with EDTA. The substantivity of MTAD was significantly greater for MTAD than for CHX and NaOCl.

Tetraclean: Tetraclean is a mixture of doxycycline hyclate. Tetraclean is able to eliminate microorganisms and the smear layer in dentinal tubules of infected root canals with a final 5-min rinse. However, treatment with Tetraclean® caused a high degree of biofilm disgregation in every considered time interval as compared with MTAD. Treatment with Tetraclean caused a high degree of biofilm disaggregation at each time interval when compared with MTAD.

Clindamycin : Clindamycin is effective against many of the endodontic pathogens. It is an efficient antimicrobial detergent.

Phenol and phenol-derivatives : A number of **phenolic derivatives** have been extensively used in dentistry for many years. Phenolic compounds possess strong antibacterial properties, and halogenation intensifies their antimicrobial activities. Phenol is believed to act by disrupting lipid-containing bacterial membranes, resulting in leakage of cellular contents. At high concentrations, these compound act by precipitating the cytoplasmic cell proteins. At lower concentrations, phenolic compound inactivate essential enzyme systems and may also cause bacterial cell wall lysis. At very low concentrations, phenolic compound inactivates essential enzyme systems and may also cause bacterial cell wall lysis. Combination of medicaments may produce additive or synergistic effects. $Ca(OH)_2$ is acting on the bacterial cytoplasmic membrane, on protein denaturation, inducing damages to the DNA.

Phenol and phenol-derivatives have been used as inter-appointment intracanal medicaments. The combination of high toxicity and limited clinical effectiveness exclude the phenol-based compound from the recommended list of contemporary

intracanal antibacterial medicaments. It is used at very low concentrations (1:5 dilution of Buckley's formula containing 19% formaldehyde and 35% cresol during pulpotomy procedures in children) [19].

Triclosan and Gantrez®: Triclosan is a broad-spectrum antimicrobial agent, active against gram-positive and gram-negative bacteria. Evaluation of the minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) of triclosan and triclosan with Gantrez® seems efficient against *P intermedia*, *F nucleatum*, *A naeslundii*, *P gingivalis*, and *E faecalis*. The MBC of triclosan with Gantrez® ranged from <0.3-10.4 µg/ml. The addition of Gantrez® enhanced the bactericidal activity of triclosan. Both triclosan and triclosan with Gantrez® demonstrated bactericidal activity against the five specific endodontic pathogens.

Metronidazole: Metronidazole is a nitroimidazole compound that exhibits a broad spectrum of activity against protozoa and anaerobic bacteria. Known for its strong antibacterial activity against anaerobic cocci as well as Gram-negative and Gram-positive bacilli, it has been used both systemically and topically in the treatment of periodontal disease. Metronidazole readily permeates bacterial cell membranes and then binds to DNA, disrupting its helical structure, which leads to rapid cell death. Root canal disinfection with erythromycin-ethylsuccinate-metronidazole-CP was a safe and effective method to promote the healing of periapical diseases.

Ozonated Water is a chemical compound consisting of three ozone atoms. It is a powerful bactericide that can kill microorganisms effectively. It is an unstable gas, capable of oxidizing any biological entity. It was reported that ozone at low concentration (0.1 ppm) is sufficient to inactivate bacterial cells including their spores.

Although ozonated water is a powerful antimicrobial agent against bacteria, less attention has been paid to the antibacterial activity of ozonated water in bacterial biofilm and hence in root canal infection. In the root canal environment, such shockwaves could potentially disrupt bacterial biofilms, rupture bacterial cell walls, and remove smear layer and debris. Shockwave generation can also enhance the breakdown of agents such as hydrogen peroxide and ozone dissolved in water and thereby enhance their disinfecting and debriding actions.

Iodine compounds: Iodine is rapidly bactericidal, fungicidal, tuberculocidal, virucidal, and sporicidal.

Medicament vehicles: There are three main types of paste vehicles:

- a) Water-soluble substances such as water, saline, dental anaesthetics, Ringers solution, methylcellulose, carboxymethylcellulose, anionic detergent solutions (including sodium lauryl sulphate and sodium lauryl diethyleneglycol).
- b) Viscous vehicles such as glycerine, polyethyleneglycol (PEG) and propylene glycol.
- c) Oil-based vehicles such as olive oil, silicone oil, camphor (the essential oil of camphorated parachlorophenol),

metacresyl acetate, eugenol and some fatty acids (including oleic, linoleic and isostearic acids).

CONCLUSION

Systemic or topical antibiotic and/or local irrigants contribute to the disinfection of the root canal, inactivation and/or mechanical elimination of the smear layer. This is a pre-requisite to avoid re-infection and stimulate pulp repair. Topical detergents may contribute to eliminate microorganisms, odontoblast residues, and pulp debris, tightly associated within the smear layer. Calcium hydroxide, sodium hypochloride, chlorhexidine, EDTA, MTAD and other root detergents are providing a series of tools used for pulp regeneration. These steps should lead to seal the crown part of the tooth with a permanent filling, in order to prevent reinfection. Such topical therapies are mandatory to obtain a stable apexification of the root apex, sealing the apical part of the radicular pulp. The stable repair of the dental pulp is one of the aims of endodontic treatments, in order to prevent the pathology recurrence.

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