



# Antibiotics as Intracanal Medicaments: A Review

ZAHED MOHAMMADI, DMD, MSD

**ABSTRACT** Antibiotics are an extremely valuable addition to the armamentarium available to health practitioners for management of bacterial infections. Due to the potential risk of adverse systemic effects of systemic applications and ineffectiveness of systemic antibiotics in the necrotic pulpless tooth and the periradicular tissues, local application of antibiotics may be a more effective mode for delivering antibiotics to infected root canals. This paper reviews the history, rationale, and applications of antibiotics and antibiotics-containing medicaments in endodontics.

## AUTHOR

**Zahed Mohammadi, DMD, MSD**, is an assistant professor, Department of Endodontics, Sadoughi University of Medical Sciences, Yazd, Iran.

The essential role of microorganisms in development and perpetuation of pulpal and periapical diseases have clearly been demonstrated in animal models and human studies.<sup>1-3</sup> Elimination of microorganisms from infected root canals is a complicated task. Numerous measures have been described to reduce the numbers of root canal microorganisms, including the use of various instrumentation techniques, irrigation regimens, and intracanal medicaments.

There is no solid evidence in the literature that mechanical instrumentation alone results in a bacteria-free root canal system. Considering the complex anatomy of root canal pulp space, this is not surprising.<sup>4</sup> On the contrary, there is in vitro and clinical evidence that mechanical instrumentation leaves significant portions of the root canal

walls untouched.<sup>5</sup> Hence, complete elimination of bacteria from the RCS by instrumentation alone is unlikely to be achieved.<sup>6</sup> Therefore, some sort of irrigation/disinfection is necessary to kill microorganisms. Simply, chemical treatment of the root canal can be arbitrarily divided into irrigants, rinses, and intervisit medicaments. Several studies have been conducted on antibiotics as root canal irrigants and medicaments.

## History

Antibiotics were first discovered in 1928 but were not routinely used clinically until the early 1940s during the World War II. Prior to this, most wartime deaths were due to bacterial infections of wounds rather than wounds themselves. The use of antibiotics was popularized as a result of the rapid recovery of wounded military personnel and this popularity

continued after the end of the war.<sup>7</sup>

Antibiotics have been an extremely valuable addition to the armamentarium available to health practitioners for management of bacterial infections. There is no doubt they have often been used to save lives that would otherwise have been lost if antibiotics had not been available. For several decades antibiotics have been prescribed in different disciplines of medicine and dentistry.<sup>7</sup> In endodontics and dental traumatology, antibiotics may be applied systemically (orally and parenterally) and locally.

The first reported local use of an antibiotic in endodontic treatment was in 1951 when Grossman used a polyan antibiotic paste known as PBSC (penicillin, bacitracin, streptomycin, and caprylate sodium).<sup>8</sup> PBSC contained penicillin to target gram-positive organisms, bacitracin for penicillin-resistant strains, streptomycin for gram-negative organisms, and caprylate sodium to target yeasts. These compounds were all suspended in a silicone vehicle. Later, nystatin replaced caprylate sodium as an antifungal agent in a similar medicament, PBSN.<sup>9</sup>

### Rationale for Local Applications of Antibiotics

While systemic antibiotics appear to be clinically effective as an adjunct in certain surgical and nonsurgical endodontic cases, their administration is not without the potential risk of adverse systemic effects, particularly possibilities of allergic reactions, toxicity, side effects, and development of resistant strains of microbes. Also, systemic administration of antibiotics relies on the circulation to bring an active drug to an infected site that may no longer possess a normal vasculature, including the necrotic pulpless tooth and the periradicular tissues. Therefore, local application of antibiotics may be a more effective mode for delivering antibiotics.<sup>10</sup>

### Ledermix

Ledermix is a glucocorticosteroid-antibiotic compound. Ledermix paste was developed by Schroeder and Triadan in 1960 and was released for sale in Europe by Lederle Pharmaceuticals in 1962.<sup>11</sup> The primary interest of Schroeder and Triadan in the development of Ledermix paste was based on the use of corticosteroid to control pain and inflammation.<sup>11</sup> The sole reason for adding the antibiotic component to Ledermix was to compensate for what was perceived to be a possible corticoid-induced reduction in the host immune response.

### LOCAL APPLICATION

of antibiotics  
may be a more  
effective mode  
for delivering  
antibiotics.

Schroeder and Triadan initially incorporated chloramphenicol in their first trials but when Lederle Pharmaceuticals became the manufacturer, the antibiotic was changed to demeclocycline HCl. Today, Ledermix paste remains a combination of the same tetracycline antibiotic, demeclocycline HCl (at a concentration of 3.2 percent), and a corticosteroid, triamcinolone acetone (concentration 1 percent), in a polyethylene glycol base.<sup>11</sup>

The two therapeutic components of the Ledermix (i.e., triamcinolone and demeclocycline) are capable of diffusing through dentinal tubules and cementum to reach the periodontal and periapical tissues.<sup>12</sup> Abbott et al. showed dentinal tubules were the major supply route of the active components to the periradicular

tissues, while the apical foramen was not as significant as a supply route.<sup>13</sup> Various factors can affect the supply of the active components to the periradicular tissues. These include the presence or absence of the smear layer, the presence or absence of cementum, and the presence of other materials within the canal, for example, calcium hydroxide.

The concentration of demeclocycline within the Ledermix paste itself (i.e., as it would be when placed within the root canal) is high enough to be effective against susceptible species of bacteria. However, within the peripheral parts of the dentine and in the periradicular tissues, the concentration achieved through diffusion is insufficient to inactivate bacteria, especially over time.<sup>14</sup> Immediately adjacent to the root canal, inhibitory levels of demeclocycline are achieved for all reported bacteria within the first day of application but this level drops to about one-tenth of the initial level after one week in both the midroot and the apical third levels. Further, away from the root canal toward the cementum, the concentration of demeclocycline after one day is not high enough to inhibit growth of 12 of the 13 strains of commonly reported endodontic bacteria.<sup>14</sup>

Heling and Pecht evaluated the efficacy of the Ledermix paste in the disinfection of dentinal tubules.<sup>15</sup> Their findings showed that Ledermix and 3 percent tetracycline in a hydrous base were effective in reducing the amount of *Staphylococcus aureus* in dentinal tubules after seven days of incubation and also after recontamination. They were not effective after 24 hours.

Abbott showed that the intradental use of the Ledermix paste and Ledermix cement is unlikely to result in any systemic side effects.<sup>16</sup> Pierce et al. demonstrated histologically that the Ledermix eliminated experimentally induced external inflammatory root resorption in vivo.<sup>17</sup> They also found that the Ledermix paste had no

damaging effects upon the periodontal membrane and that this paste was an effective medication for the treatment of progressive root resorption in traumatically injured teeth. Taylor et al. evaluated effects of Ledermix paste and Pulpdent paste on mouse fibroblasts and on bacteria in vitro.<sup>18</sup>

Dilutions of Ledermix paste, Pulpdent paste and a mixture of equal parts by weight of Ledermix paste and Pulpdent paste were added to in vitro cultures of mouse fibroblasts or bacteria for 24 hours, and various cell functions were then examined: mitosis in and survival of fibroblasts, and survival of *Lactobacillus casei* or *Streptococcus mutans*. Ledermix was found to reversibly inhibit mitosis

while present in the concentrations range  $10^{-3}$  to  $10^{-6}$  mg/ml. Mixing with Pulpdent did not modify this antimitotic effect. Ledermix killed mouse fibroblasts at  $10^{-3}$  mg/ml and above, while Pulpdent killed at 1 mg/ml and above.

The toxic effect of Ledermix was slightly inhibited by mixing it with Pulpdent. Ledermix killed *S. mutans* at about the same concentration at which it killed the mammalian cells, but required a one thousand-fold greater concentration to kill *L. casei*. Pulpdent killed both *L. casei* and *S. mutans* at approximately one-fifth of the concentration at which it killed the mammalian cells. Thong et al. compared the effect of calcium hydroxide (Pulpdent) and Ledermix paste

on periodontal healing and root resorption following replantation histomorphometrically.<sup>19</sup> They found that periodontal ligament inflammation and inflammatory root resorption were markedly inhibited by both calcium hydroxide and corticosteroid-antibiotic relative to untreated controls.

Replacement resorption was lowest in the corticosteroid-antibiotic group, and significantly more normal periodontal ligament was present in this group than in calcium hydroxide and control groups. Wong and Sae-Lim evaluated the effect of immediate intracanal Ledermix on root resorption of delayed-replanted monkey teeth.<sup>20</sup> For the experimental group, intracanal Ledermix was placed

prior to extraction and replantation after one-hour bench dry. The positive control group was root filled and replanted after one hour while the negative control group was root filled and replanted immediately.

The negative control group produced highly significant favorable healing and unfavorable healing as compared to the Ledermix group. The Ledermix group only showed significantly higher occurrence of complete healing (35.46 percent) compared to the positive control group (16.58 percent), but there were no significant differences in the inflammatory root resorption and replacement resorption. Nevertheless, when the latter two unfavorable healing patterns were combined, there was a significantly lower overall unfavorable healing in the Ledermix group (64.54 percent) when compared to the positive control group (83.43 percent). This unfavorable healing outcome in the Ledermix group, however, was not significantly different from the favorable healing outcome with the same treatment modality. Bryson et al. evaluated the effect of immediate intracanal placement of Ledermix paste(R) on healing of replanted dog teeth after extended dry times (one hour).<sup>21</sup> Their finding showed that the Ledermix paste-treated roots had statistically significantly more healing and less resorption than the roots treated with  $\text{Ca(OH)}_2$ .

Root filling with the Ledermix paste also resulted in significantly less loss in root mass due to resorption compared to those roots filled with  $\text{Ca(OH)}_2$ . Chen et al. evaluated the individual influence of triamcinolone and demeclocycline on external root resorption after extended extraoral dry time (one hour).<sup>22</sup> Their findings showed that the groups treated with Ledermix, triamcinolone, and demeclocycline had statistically significantly more favorable healing than the group filled with gutta percha replanted after one-hour dry time (positive control). There was no

statistically significant difference between the Ledermix group and the triamcinolone group, while the tetracycline group showed less favorable healing than the negative control, the Ledermix group, and the triamcinolone group. They concluded that corticosteroid and tetracycline, as anti-inflammatory and antiresorptive agents, shut down or minimized the inflammatory reaction including clastic-cells mediated resorption, thus promoted more favorable healing than the positive control group, which had no intracanal medicaments.

Furthermore, they forecasted that in severe traumatic injuries, where a large sur-

### ROOT FILLING WITH the Ledermix paste also resulted in significantly less loss in root mass due to resorption compared to those roots filled with $\text{Ca(OH)}_2$ .

face area of periodontal inflammation is expected, removing the pulp and placing corticosteroids into the canal at the emergency visit will become a standard protocol.<sup>22</sup>

Trope evaluated the relationship of intracanal medicaments to endodontic flare-ups.<sup>23</sup> Formocresol, Ledermix, and calcium hydroxide were placed in strict sequence irrespective of the presence or absence of symptoms or radiographic signs of apical periodontitis. He found no significant difference in the flare-up rate among the three intracanal medicaments. Ehrmann et al. investigated the relationship of postoperative pain to three different medicaments placed in the root canal after a complete biomechanical debridement of the root canal system in patients presenting for emergency

relief of pain.<sup>24</sup> They found that painful teeth with acute apical periodontitis that had been dressed with Ledermix paste gave rise to less pain than that experienced by patients who had a dressing of calcium hydroxide, or no dressing at all.

Kim et al. investigated the effects of the Ledermix paste as an intracanal medicament on discoloration of mature teeth, whether the discoloring effects were related to the method of application, as well as the effects of sunlight upon discoloration of mature teeth.<sup>25</sup> Results demonstrated that after 12 weeks, sunlight exposure had caused dark grey-brown staining of the teeth in the Ledermix groups, but this did not occur when the teeth were kept in the dark. More severe staining was noted when Ledermix paste filled the pulp chamber than when the paste was restricted to below the CEJ.

They suggested that if placement of the Ledermix was restricted to below the gingival margin, such effects could be minimized. In another study, they investigated the effects of the Ledermix paste as an intracanal medicament on discoloration of mature teeth, whether the discoloring effects were related to the method of application, as well as the effects of sunlight upon discoloration of immature teeth. After 12 weeks, sunlight exposure had caused dark grey-brown staining in the Ledermix groups but this did not occur when the teeth were kept in the dark. More severe staining was noted when Ledermix paste filled the pulp chamber than when the paste was restricted to below the CEJ and when teeth were exposed to sunlight.<sup>26</sup>

When compared to the results of a similar study using mature teeth, the results were similar but the immature teeth were more severely stained than the mature teeth. The  $\text{Ca(OH)}_2$  paste caused an increase in lightness and yellowness in immature teeth.<sup>26</sup>

## Combination of Ledermix and Calcium Hydroxide

The combination of Ledermix paste with calcium hydroxide was advocated by Schroeder initially for the treatment of necrotic teeth with incomplete root formation.<sup>11</sup> A 50-50 mixture of Ledermix paste and calcium hydroxide has also been advocated as an intracanal dressing in cases of infected root canals, pulp necrosis and infection with incomplete root formation (as an initial dressing prior to using calcium hydroxide alone for apexification), perforations, inflammatory root resorption, inflammatory periapical bone resorption, and for treatment of large periapical radiolucent lesions.<sup>12</sup> It has been shown that the 50-50 mixture results in slower release and diffusion of the active components of Ledermix paste, which makes the medicament last longer in the canal.<sup>27</sup> This in turn helps to maintain the sterility of the canal for longer and also maintains a higher concentration of all components within the canal.<sup>27</sup>

The 50-50 mixture of Ledermix paste and calcium hydroxide paste does not alter the pH to any noticeable extent and therefore it is expected that the mixture will act in a similar manner to when calcium hydroxide is used alone. Taylor et al. also showed that for two indicator micro-organisms, *L. casei* and *S. mutans* (which are cariogens), the 50-50 mixture was marginally more effective than either paste used alone.<sup>18</sup> However, Seow showed that for *S. sanguis* and *S. aureus*, the addition of only 25 percent by volume of Calylx (a calcium hydroxide in saline paste) (Otto and Co., Frankfurt, Germany) to Ledermix converted the zone of complete inhibition originally seen in Ledermix to one of only partial inhibition.<sup>28</sup> This latter study suggested that some medicaments should not be used in combination, and that when two medicaments with strong antimicrobial activity are combined there may be no additive or synergistic effects.<sup>28</sup>

Chu et al. compared the efficacy of disinfection of root canals with periapical radiolucencies when treated with either antibiotics/steroid medicaments (Ledermix or Septomixine) or a calcium hydroxide paste (Calasept, Speiko, Darmstadt, Germany).<sup>29</sup> Their finding showed that in the Ledermix group, 38 strains of bacteria were recovered. The Septomixine group had 25 strains, and the Calasept group had 25 strains. Gram-positive facultative anaerobic cocci (including *staphylococci* and *streptococci*) were more prevalent than the gram-negative obligate anaerobic rods after treatment in all three groups.

THE CLINDAMYCIN  
paste was successful in  
eliminating  
bacterial growth in  
21 of 25 teeth tested by  
the 14th day.

## Septomixine Forte

Septomixine Forte (Septodont, Saint-Maur, France) contains two antibiotics: — neomycin and polymyxin B sulphate. Neither of these can be considered as suitable for use against the commonly reported endodontic bacteria because of their inappropriate spectra of activity.<sup>14</sup> Neomycin is bactericidal against gram-negative bacilli but it is ineffective against bacteroides and related species, as well as against fungi. Polymyxin B sulphate is ineffective against gram-positive bacteria, as shown by Tang et al., who demonstrated that a routine one-week application of Septomixine Forte was not effective in inhibiting residual intracanal bacterial growth between appointments.<sup>30</sup> In addition, although the anti-inflammatory (corticosteroid) agent, dexamethasone

(at a concentration of 0.05 percent), is clinically effective, triamcinolone is considered to have less systemic side effects.

## Clindamycin

Clindamycin is effective against many of the representative endodontic pathogens, including *actinomyces*, *eubacterium*, *fusobacterium*, *propionobacterium*, *microaerophilic streptococci*, *peptococcus*, *peptostreptococcus*, *veillonella*, *prevotella*, and *porphyromonas*. It is particularly effective in vitro against black-pigmented *prevotella* and *porphyromonas* species.<sup>10</sup>

Molander et al. investigated the effect of clindamycin on root canal infection when placed as an intracanal dressing.<sup>31</sup> A 150 mg clindamycin capsule was mixed with sterile water and placed into infected root canals. Following initial bacteriological sampling and routine instrumentation, clindamycin powder mixed to a paste with saline was applied for 14 days. The presence or absence of bacteria was determined in samples taken immediately after removal of the dressing, and after a period of seven days during which the canals were filled with sampling fluid. The results indicated that clindamycin offered no advantage over conventional root canal dressings, such as calcium hydroxide. However, the concentration of the active drug and its ability to penetrate deeply into the root canal system was not clear. Also, no negative controls were used.

Nonetheless, the clindamycin paste was successful in eliminating bacterial growth in 21 of 25 teeth tested by the 14th day. In the four remaining teeth, *enterococci* constituted the dominant flora despite antibiotic treatment. Gilad et al. evaluated the efficacy of clindamycin in an ethylene vinyl acetate, EVA, vehicle in reducing bacterial growth in vitro.<sup>10</sup> Clindamycin fibers were manufactured as follows: 0.075 g of calcium phosphate monobasic was combined with 10 ml of distilled water, and was added to a solution consisting of 0.050 g of clindamy-

cin phosphate and 10 ml of distilled water. The combined solution was then lyophilized for 24 hours, and the resultant powder was filtered to achieve a uniform particle size of 45 microns. The powder (125 mg) was combined with 375 mg of EVA particles and was processed through an extrusion plastometer at diameters of 2 mm, 1 mm, and 0.5 mm.

The final extrusion produced a 250 mm-long fiber, with a calculated approximate dose of 0.2 mg of clindamycin/mm fiber. Results of the bacterial sensitivity test demonstrated that at the concentration of 10 microgram/ml, all bacteria tested showed varying degrees of inhibition, especially *P. intermedia*, followed by *F. nucleatum*, *P. micros*, and *S. intermedius*. They also found that clindamycin/EVA fibers significantly reduced the number of bacteria present in extracted human teeth. Furthermore, clindamycin/EVA fibers demonstrated the ability to release active drug for at least two weeks.

Lin et al. compared the antibacterial effect of clindamycin and tetracycline in bovine dentinal tubule model, as well as using the agar diffusion test.<sup>32</sup> Their findings showed that clindamycin significantly reduced the amount of viable bacteria in each dentin layer compared with the tetracycline. The agar diffusion test, wherein dilutions in increments of 1/3 and 1/9 were used, revealed that both medicaments had antibacterial activity, but clindamycin was significantly better. In the 1/27 dilution, clindamycin had a minor effect and tetracycline had no effect at all.

### Triple Antibiotic Paste

The infection of the root canal system is considered to be a polymicrobial infection, consisting of both aerobic and anaerobic bacterial. Because of the complexity of the root canal infection, it is unlikely that any single antibiotic could result in effective sterilization of the canal. More likely a combination would

be needed to address the diverse flora encountered. A combination of antibiotics would also decrease the likelihood of the development of resistant bacterial strains.

The combination that appears to be most promising consists of metronidazole, ciprofloxacin, and minocycline.<sup>33,34</sup> Sato et al. evaluated the potential of a mixture of ciprofloxacin, metronidazole and minocycline to kill bacteria in the deep layers of root canal dentine in situ.<sup>35</sup> Results showed that no bacteria were recovered from the infected dentine of the root canal wall 24 hours after application of the drug

**THE COMBINATION  
that appears to be  
most promising consists  
of metronidazole,  
ciprofloxacin, and  
minocycline.**

combination, except in one case in which a few bacteria were recovered.

Hoshino et al. investigated the antibacterial effect of a mixture of ciprofloxacin, metronidazole, and minocycline, with and without the addition of rifampicin, on bacteria taken from infected dentine of root canal walls.<sup>36</sup> The efficacy was also determined against bacteria of carious dentine and infected pulps, which may be precursory bacteria of infected root dentine. They found that alone, none of the drugs resulted in complete elimination of bacteria. However, in combination, these drugs were able to consistently sterilize all samples. Iwaya et al. reported a necrotic immature mandibular second premolar with periapical involvement and sinus tract.<sup>37</sup>

Instead of the standard root canal treat-

ment protocol and apexification, antimicrobial agents (metronidazole and ciprofloxacin) were used in the canal, after which the canal was left empty. Radiographic examination showed the start of apical closure five months after the completion of the antimicrobial protocol. Thickening of the canal wall and complete apical closure was confirmed 30 months after the treatment, indicating the revascularization potential of a young permanent tooth pulp into a bacteria-free root canal space. Takushige et al. evaluated the efficacy of poly-antibiotic paste consisted of ciprofloxacin, metronidazole, and minocycline, on the clinical outcome of so-called "Lesion Sterilization and Tissue Repair," LSTR, therapy in primary teeth with periradicular lesions.<sup>38</sup> Results showed that in all cases, clinical symptoms such as gingival swelling, sinus tracts, induced dull pain, spontaneous dull pain, and pain on biting disappeared after treatment, although in four cases clinical signs and symptoms were finally resolved only after retreatment using the same procedures. Thus, gingival abscesses and fistulae, if present, disappeared after a few days.

Successor permanent teeth erupted without any disorders or were found radiographically to be normal and in the process of eruption. All the cases were evaluated as successful. The mean function time of the primary teeth was 680 days (range: 68 – 2,390 days), except for one case in which the successor permanent tooth was congenitally missing. Windley et al. assessed the efficacy of a triple antibiotic paste in the disinfection of immature dog teeth with apical periodontitis.<sup>33</sup> The canals were sampled before (S1) and after (S2) irrigation with 1.25 percent NaOCL and after dressing with a triple antibiotic paste (S3), consisting of metronidazole, ciprofloxacin, and minocycline. At S1, 100 percent of the samples cultured positive for bacteria with a mean CFU count of 1.7 x 10. At S2, 10 percent of the samples cultured bacteria-free with a mean CFU count of 1.4 x

10. At S<sub>3</sub>, 70 percent of the samples cultured bacteria-free with a mean CFU count of only 26. Reductions in mean CFU counts between S<sub>1</sub> and S<sub>2</sub>, as well as between S<sub>2</sub> and S<sub>3</sub>, were statistically significant.

### Metronidazole

Metronidazole is a nitroimidazole compound that exhibits a broad spectrum of activity against protozoa and anaerobic bacteria. Known for its strong antibacterial activity anaerobic cocci, as well as gram-negative and gram-positive bacilli, it has been used both and topically in the treatment of periodontal disease. Metronidazole readily permeates bacterial cell membranes. It then binds to DNA, disrupting its helical

structure, and leads to very rapid cell death (65). Roche and Yoshimori investigated the activity of metronidazole against clinical isolates from odontogenic abscesses in vitro.<sup>39</sup> Their findings showed that metronidazole had excellent activity against anaerobes isolated from odontogenic abscesses but had no activity against aerobes.

Siqueira and de Uzeda evaluated the antibacterial activity of 0.12 percent chlorhexidine gel; 10 percent metronidazole gel; calcium hydroxide plus distilled water, calcium hydroxide plus camphorated para-mono-chlorophenol (CPMC); and calcium hydroxide plus glycerin using agar diffusion test.<sup>40</sup> The results revealed that calcium hydroxide/CPMC paste was effective against

all bacterial strains tested. Chlorhexidine was also inhibitory to all strains. It was about as effective as calcium hydroxide/CPMC paste against most of the strains.

Metronidazole also caused inhibition of growth of all obligate anaerobes tested and was more effective than calcium hydroxide/CPMC against two strains. In another study, Lima et al. evaluated the effectiveness of chlorhexidine- or antibiotics-based medications in eliminating *E. faecalis* biofilms.<sup>41</sup> They found there were significant differences between the formulations tested. The association of clindamycin with metronidazole significantly reduced the number of cells in one-day biofilms. However, of all medications tested, only 2 percent

chlorhexidine-containing medications were able to thoroughly eliminate most of both one-day and three-day *E. faecalis* biofilms.

Wang et al. evaluated the effect of metronidazole-chlorhexidine solution on treatment of chronic apical periodontitis.<sup>42</sup> They found that the effective rate of metronidazole-chlorhexidine solution treatment was 97.6 percent. Yu et al. evaluated the effect of a paste made of erythromycin ethylsuccinate, metronidazole and CP to sterilize the root canal.<sup>43</sup> The clinical observation of 180 patients with entirely developed root apex of acute and chronic apical periodontitis showed that there was no significant difference comparing erythromycin-ethylsuccinate-metronidazole-CP with formocresol in root canal sterilization. Therefore, the irritability and poisonousness of the paste could be reduced by using erythromycin-ethylsuccinate-metronidazole-CP instead of FC.

They concluded that the root canal sterilization with erythromycin-ethylsuccinate-metronidazole-CP was a safe and effective method to promote the restoration of root apex diseases.<sup>43</sup> Gao et al. investigated a sustained release delivery gutta percha point containing metronidazole, SRDGM, for root canal disinfection, and determined the drug concentration in vitro and the time that the device maintained the effective drug concentration.<sup>44</sup> Their findings showed that the SRDGM contained metronidazole 2013 micrograms; it could release 68.24 percent of the total drug in 24 hours in vitro. The effective metronidazole concentration released lasted more than 10 days. On the 10th day, there was also 33.13 microg/ml metronidazole released, which was more than a minitory inhibitory concentration of metronidazole.

Hoelscher et al. evaluated the antimicrobial effects of five antibiotics (amoxicillin, penicillin, clindamycin, metronidazole, and doxycycline) when added to Kerr Pulp Canal Sealer EWT against *E. faecalis*.<sup>45</sup> They found that all mentioned antibiotics,

except for metronidazole, could enhance the antimicrobial efficacy of the sealer. Krithikadatta et al. evaluated the disinfection of dentinal tubules using 2 percent chlorhexidine gel, 2 percent metronidazole gel, bioactive glass (S53P4) in comparison with calcium hydroxide.<sup>46</sup> Their finding demonstrated that the overall percentage inhibition of bacterial growth (at 200 microm and 400 microm depth) was 100 percent with 2 percent chlorhexidine gel. The inhibition of growth was moderate with 2 percent metronidazole gel (86.5 percent), followed by bioactive glass (62.8 percent) and calcium hydroxide (58.5 percent).

**GASTROINTESTINAL  
side effects are  
common among many  
medications, but in  
particular macrolide  
antibiotics.**

### Potential Side Effects

As clinicians make decisions on whether or not to prescribe antibiotics in conjunction with endodontic treatment, it is important to be cognizant of the risks and side effects of antibiotics. The use of antibiotics is not different from any other medications in that the benefits of using them must outweigh the risks involved, from the perspectives of both the direct treatment of patients and global public health issues. Among the well-documented side effects to antibiotics commonly prescribed for endodontic infections are hypersensitivity reactions and drug fevers to penicillin and other  $\beta$ -lactam antibiotics, pseudomembranous colitis, which occasionally occurs with clindamycin or other antibiotics, nausea, vomiting, and gastrointestinal distress

common with macrolides, photosensitivity that may accompany tetracycline and renal toxicity that may be associated with the use of aminoglycosides.<sup>47</sup>

Hypersensitivity side effects are more common among  $\beta$ -lactam antibiotics, and, while drug rash, serum sickness, and anaphylactic reactions are well-recognized by clinicians, drug fevers are the most common antibiotic-mediated hypersensitivity side effect.<sup>47</sup> Drug fevers account for 10-15 percent of unexplained fevers in hospitalized patients in the United States, and may occur with any medication, but are common with  $\beta$ -lactams and sulfonamides.<sup>47</sup> Gastrointestinal side effects are common among many medications, but in particular macrolide antibiotics. Clarithromycin (such as Biaxin XL) and azithromycin are associated with less GI irritation than erythromycin.<sup>48</sup>

Diarrhea is a frequent symptom of GI distress in patients on macrolides,  $\beta$ -lactams or clindamycin, and may be a direct irritation of the intestinal mucosa or an imbalance in intestinal flora. As was noted before, one type of complication of antibiotics due to the microbial imbalance is the overgrowth of clostridium difficile, causing pseudomembranous colitis, a rare but serious condition. This condition can develop up to six weeks after cessation of therapy and is usually caused by clindamycin, ampicillin or cephalosporins, especially in hospitalized patients.<sup>48-50</sup>

One of the most serious side effects of the frequent, indiscriminate use of antibiotics, not only for the individual patient but also from a global public health perspective, is the development of resistant bacterial strains.<sup>51-54</sup> As noted before, the percentage of  $\beta$ -lactamase-positive bacteria tends to increase in endodontic infections in patients with prior use of  $\beta$ -lactam antibiotics.<sup>55</sup>

Another group of microorganisms that is becoming among the most serious drug-resistant bacteria is *enterococci*.

*Enterococci*, particularly *E. faecalis* and *E. faecium*, were shown to be the most prevalent among the microflora of root canals in failing endodontic cases.<sup>55</sup>

## Conclusions

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. Ledermix, a glucocorticosteroid-antibiotic compound, has anti-inflammatory, antibacterial and antiresorptive properties, all of which help to reduce the periapical inflammatory reaction including clastic-cell mediated resorption. This material has been shown to significantly lower the incidence of inflammatory and replacement resorption, and thus prompts more favorable healing in replanted teeth.

3. A 50:50 mixture of Ledermix paste and calcium hydroxide has been advocated as an intracanal dressing in cases of pulpless infected root canals, pulp necrosis and infection with incomplete root formation (apexification), perforations, inflammatory root resorption, inflammatory periapical bone resorption, and for the treatment of large periapical radiolucent lesions.

4. Clindamycin alone or in an ethylene vinyl acetate vehicle can reduce the bacterial load inside the root canal system (including dentinal tubules) significantly.

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.

6. Among the well-documented side effects to antibiotics commonly prescribed for endodontic infections (penicillins) are hypersensitivity reactions and drug fevers. ■■■■■

## REFERENCES

1. Kakehashi S, Stanley HR, Fitzgerald RJ, The effects of surgical exposure of dental pulps in germ-free and conventional

laboratory rats. *Oral Surg* 18:340-8, 1965.

2. Möller AJ, Fabricius L, et al, Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys. *Scand J Dent Res* 89:475-84, 1981.

3. Sundqvist G, Ecology of the root canal flora. *J Endod* 18:427-30, 1992.

4. Hess W, Anatomy of root canals in the teeth of the permanent dentition, New York, William Wood & Co., 1925.

5. Peters OA, Laib A, et al, Changes in root canal geometry after preparation assessed by high resolution computed tomography. *J Endod* 27:1-6, 2001.

6. Byström A, Sundqvist G, Bacteriologic evaluation of the efficacy of mechanical root canal instrumentation in endodontic therapy. *Scand J Dent Res* 89:321-28, 1981.

7. Abbott PV, Selective and intelligent use of antibiotics in endodontics. *Aust Endod J* 26:30-9, 2000.

8. Grossman LI, Polyantibiotic treatment of pulpless teeth. *J Am Dent Assoc* 43:265-78, 1951.

9. Weine FS, Endodontic Therapy, third ed., Mosby, p. 325, 1982.

10. Gilad JZ, Teles R, et al, Development of a clindamycin-impregnated fiber as an intracanal medication in endodontic therapy. *J Endod* 25:722-7, 1999.

11. Athanassiadis B, Abbott PV, Walsh LJ, The use of calcium hydroxide, antibiotics and biocides as antimicrobial medications in endodontics. *Aust Dent J* 52:564-582, 2007.

12. Abbott PV, Medicaments: aids to success in endodontics. Part 1. A review of literature. *Aust Dent J* 35:438-48, 1990.

13. Abbott PV, Heithersay GS, Hume WR, Release and diffusion through human tooth roots in vitro of corticosteroid and tetracycline trace molecules from Ledermix paste. *Endod Dent Traumatol* 4:55-62, 1988.

14. Abbott PV, Hume WR, Pearman JM, Antibiotics and endodontics. *Aust Dent J* 35:50-60, 1990.

15. Helling I, Pecht M, Efficacy of Ledermix paste in eliminating *Staphylococcus aureus* from infected dentinal tubules in vitro. *Endod Dent Traumatol* 7:251-4, 1991.

16. Abbott PV, Systemic release of corticosteroids following intra-dental use. *Int Endod J* 25:189-91, 1992.

17. Pierce A, Heithersay G, Lindsog S, Evidence for direct inhibition of dentinoclasts by a corticosteroid/antibiotic endodontic paste. *Endod Dent Traumatol* 4:44-45, 1988.

18. Taylor MA, Hume WR, Heithersay GS, Some effects of Ledermix paste and Pulpdent paste on mouse fibroblasts and on bacteria in vitro. *Endod Dent Traumatol* 5:266-73, 1989.

19. Thong YL, Messer HH, et al, Periodontal response to two intracanal medicaments in replanted monkey incisors. *Dent Traumatol* 17:254-9, 2001.

20. Wong KS, Sae-Lim V, The effect of intracanal Ledermix on root resorption of delayed-replanted monkey teeth. *Dent Traumatol* 18:309-15, 2002.

21. Bryson E, Levin L, et al, Effect of immediate intracanal placement of Ledermix paste on healing of replanted dog teeth after extended dry times. *Dent Traumatol* 18:316-21, 2002.

22. Chen H, Teixeira FB, et al, The effect of intracanal anti-inflammatory medicaments on external root resorption of replanted dog teeth after extended extra-oral dry time. *Dent Traumatol* 24:74-8, 2008.

23. Trope M, Relationship of intracanal medicaments to endodontic flare-ups. *Endod Dent Traumatol* 6:226-9, 1990.

24. Ehrmann EH, Messer HH, Adams GG, The relationship of intracanal medicaments to postoperative pain in endodontics.

*Int Endod J* 36:868-75, 2003.

25. Kim ST, Abbott PV, McGinley P, The effects of Ledermix paste on discoloration of mature teeth. *Int Endod J* 33:227-32, 2000.

26. Kim ST, Abbott PV, McGinley P, The effects of Ledermix paste on discoloration of immature teeth. *Int Endod J* 33:233-7, 2000.

27. Abbott PV, Hume WR, Heithersay GS, Effect of combining Ledermix and calcium hydroxide pastes on the diffusion of corticosteroid and tetracycline through human tooth roots in vitro. *Endod Dent Traumatol* 5:188-92, 1989.

28. Seow WK, The effects of dyadic combinations of endodontic medicaments on microbial growth inhibition. *Red Dent* 12:292-7, 1990.

29. Chu FC, Leung WK, et al, Identification of cultivable microorganisms from root canals with apical periodontitis following two-visit endodontic treatment with antibiotics/steroid or calcium hydroxide dressings. *J Endod* 32:17-23, 2005.

30. Tang G, Samaranyake LP, Yip HK, Molecular evaluation of residual endodontic microorganisms after instrumentation, irrigation and medication with either calcium hydroxide or Septomixine. *Oral Dis* 10:389-97, 2004.

31. Molander A, Dahlen G, Evaluation of the antibacterial potential of tetracycline or erythromycin mixed with calcium hydroxide as intracanal dressing against *E. faecalis* in vivo. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 96:744-50, 2003.

32. Lin S, Levin L, et al, Reduction of viable bacteria in dentinal tubules treated with clindamycin or tetracycline. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 96:751-6, 2003.

33. Windley W 3rd, Teixeira F, et al, Disinfection of immature teeth with a triple antibiotic paste. *J Endod* 31:439-43, 2005.

34. Trope M, Treatment of immature teeth with nonvital pulps and apical periodontitis. *Endod Topics* 14: 51-9, 2006.

35. Sato I, Ando-Kurihara N, et al, Sterilization of infected root canal dentine by topical application of a mixture of ciprofloxacin, metronidazole and minocycline in situ. *Int Endod J* 29:118-24, 1996.

36. Hoshino E, Ando-Kurihara N, et al, In vitro antibacterial susceptibility of bacteria taken from infected root dentine to a mixture of ciprofloxacin, metronidazole and minocycline. *Int Endod J* 29:125-30, 1996.

37. Iwaya SI, Ikawa M, Kubota M, Revascularization of an immature permanent tooth with apical periodontitis and sinus tract. *Dent Traumatol* 17:185-7, 2001.

38. Takushige T, Cruz EV, et al, Endodontic treatment of primary teeth using a combination of antibacterial drugs. *Int Endod J* 37:132-8, 2004.

39. Roche Y, Yoshimori RN, In vitro activity of spiramycin and metronidazole alone or in combination against clinical isolates from odontogenic abscesses. *J Antimicrob Chemother* 40:353-77, 1997.

40. Siqueira JF Jr, de Uzeda M, Intracanal medicaments: evaluation of the antibacterial effects of chlorhexidine, metronidazole, and calcium hydroxide associated with three vehicles. *J Endod* 23:167-9, 1997.

41. Lima KC, Fava LR, Siqueira JF Jr, Susceptibilities of *Enterococcus faecalis* biofilms to some antimicrobial medications. *J Endod* 27:616-9, 2001.

42. Wang ZP, Wang D, et al, The observation of the effect of metronidazole-chlorhexidine solution on treatment of periapical periodontitis. *Shanghai Kou Qiang Yi Xue* 12:244-6, 2003.

43. Yu X, Song M, Xu L, Clinical evaluation of the paste of erythromycin ethylsuccinate-metronidazole CP for root canal sterilization. *Shanghai Kou Qiang Yi Xue* 9:143-4, 2000.
44. Gao J, Wang ZP, et al, The preparation and in vitro release test of sustained release delivery gutta percha point containing metronidazole. *Shanghai Kou Qiang Yi Xue* 13:557-60, 2004.
45. Hoelscher AA, Bahcall JK, Maki JS, In vitro evaluation of the antimicrobial effects of a root canal sealer-antibiotic combination against *Enterococcus faecalis*. *J Endod* 32:145-7, 2006.
46. Krithikadatta J, Indira R, Dorothykalyani AL, Disinfection of dentinal tubules with 2 percent chlorhexidine, 2 percent metronidazole, bioactive glass when compared with calcium hydroxide as intracanal medicaments. *J Endod* 33:1473-6, 2007.
47. Cunha BA, Antibiotic side effects. *Med Clin North Am* 85:149-85, 2001.
48. Baker KA, Fotos PG, The management of odontogenic infections. A rationale for appropriate chemotherapy. *Dent Clin North Am* 38:689-706, 1994.
49. Sensakovic JW, Smith LG, Oral antibiotic treatment of infectious diseases. *Med Clin North Am* 85:115-23, 2001.
50. Sandor GK, Low DE, et al, Antimicrobial treatment options in the management of odontogenic infections. *J Can Dent Assoc* 64:508-14, 1998.
51. Handal T, Olsen I. Antimicrobial resistance with focus on oral  $\beta$ -lactamases. *Eur J Oral Sci* 108:163-74, 2000.
52. Jenkinson HF, Ins and outs of antimicrobial resistance: era of the drug pumps. *J Dent Res* 75:736-42, 1996.
53. Harrison JW, Svec TA, The beginning of the end of the antibiotic era? Part I. The problem: Abuse of the "miracle drugs." *Quintessence Int* 29:151-62, 1998.
54. Harrison JW, Svec TA, The beginning of the end of the antibiotic era? Part II. Proposed solutions to antibiotic abuse. *Quintessence Int* 29:223-9, 1998.
55. Fouad AF, Are antibiotics effective for endodontic pain? *Endod Topics* 3:52-66, 2002.

**TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT** Zahed Mohammadi, DMD, MSD, at mohammadi\_zahed@yahoo.com.