



MICROBIOLOGIC ASPECTS OF ENDODONTIC INFECTIONS

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ABSTRACT

Our understanding of endodontic infections and treatment of endodontic disease has increased significantly over the last decade. This article is an update of those findings. Aspects that are reviewed include: portal of entry for microorganisms, virulence and pathogenicity of organisms, descriptions of primary and recurrent endodontic infections, and treatment of endodontic infections.

Virtually all endodontic disease (pulpal and periradicular) are either directly or indirectly related to the presence of microorganisms. To effectively diagnose and treat endodontic disease, clinicians must be familiar with the nature of infections of the root canal system and periradicular tissues. This fundamental relationship of microorganisms and endodontic disease has been established. Antony van Leeuwenhoek, the father of microscopy, described microorganisms observed from an infected root canal.¹ When he removed material from the hollow part of a tooth and examined it with his microscope, Leeuwenhoek saw “cavorting beasties.”

It then took about 200 years for W.D. Miller, who was working in Robert Koch’s laboratory in 1890, to make the correlation between microorganisms and pulpal/periapical disease.^{2,3} Using a microscope, Miller observed in teeth with exposed pulp chambers that the bacteria in the pulp chamber were different from those in the root canals. In addition, from culture experiments, Miller noted that only a few of the observed species of bacteria were cultivable.^{2,3} Even today many of the species remain uncultivable.⁴⁻⁷

In 1965, Kakehashi et al. showed that bacteria are etiological agents of both pulpal infection and the development of periapical lesions.⁸ Following mechanical pulp exposure, pulpal dis-

ease and periapical lesion formation occurred only in conventional rats with normal microflora but not in germ-free rats. In fact, in the absence of bacteria, the pulps of the germ-free rats formed bridges of reparative dentin demonstrating the potential for pulpal repair.⁸

Portal of Entry for Microorganisms

The most common portal of entrance for microorganisms to the pulp cavity is dental caries. In addition, microbes may find their way into the pulp cavity via mechanical or traumatic exposure and via exposed lateral/furcation canals or even exposed noncarious dentinal tubules. Once the pulp is necrotic, dentinal tubules become dead tracts that microorganisms can traverse with impunity. Passage of microbes through exposed dentinal tubules is likely the pathway when the pulp becomes necrotic following a traumatic



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injury to a tooth. Microorganisms may gain access to the pulp cavity via cracks in the enamel-dentin and periodontal exposure (treatment/disease) of dentinal tubules and accessory canals. Although it has been demonstrated in animals, a less likely route is via anachoresis in which microorganisms are transported in the blood to an area of inflammation where they establish an infection.⁹⁻¹²

Microbial Virulence and Pathogenicity

The dental pulp and periradicular tissues are normally sterile tissues. An endodontic infection results when microbes invade and multiply in the pulp cavity or periradicular tissues. Pathogenicity is the ability of microbes to produce disease while virulence is the degree of pathogenicity. Endodontic disease includes the response of these tissues to the microbes and their virulence factors. Virulence factors include capsules, pili (fimbriae) lipopolysaccharides (endotoxin), enzymes (collagenase, hyaluronidase, chondroitin sulfatase, proteases), extracellular vesicles and by-products such as polyamines, indole, hydrogen sulfide, methyl mercaptan, ammonia, butyrate and other organic acids.¹³⁻²¹ Virulence factors may vary from strain to strain even within the same species. The number of virulence factors relates to the degree of pathogenicity.

With few exceptions, studies that cultured the contents of infected pulp cavities and periradicular abscesses have shown them to be polymicrobial with 3-12 isolates. The majority of microbial isolates are a subset of organisms isolated from periodontal tissues which in turn are a subset of 400 or more species of bacteria in the oral cavity.^{5,22-25} Before the 1970s, very few strains of strict anaerobes were cultivated. Improved techniques for anaerobic culturing demonstrated that the vast majority of cultivable bacteria in root canal infections are anaerobic.²⁶⁻³⁰

Table 1

MICROBES OFTEN DETECTED IN INFECTED ROOT CANALS	
Obligate Anaerobes	Facultative Anaerobes
Gram-negative bacilli Porphyromonas* Prevotella** Fusobacterium Campylobacter Bacteroides	Gram-negative bacilli Capnocytophaga Eikenella
Gram-negative cocci Veillonella	Gram-negative cocci Neisseria
Gram-positive bacilli Actinomyces Lactobacillus Propionibacterium Bifidobacterium	Gram-positive bacilli Actinomyces Lactobacillus
Gram-positive cocci Streptococcus Peptostreptococcus	Gram-positive cocci Streptococcus Enterococcus
Spirochetes Treponema	Fungi Candida
* Dark Pigmented Bacteria ** Dark Pigmented Bacteria and Non-pigmenting Bacteria	

Primary Endodontic Infections

The dynamics of the ecosystem in infected root canals has been studied in monkeys.³¹⁻³³ Following the introduction of the monkey's indigenous oral flora into their canals, the canals were sealed but sampled over a period of 1,080 days.³² Although facultative bacteria predominate early in root canal infections, bacteria that are strict anaerobes displace them. After 1,080 days, 98 percent of the cultivable bacteria were strict anaerobes. A root canal containing a necrotic pulp becomes a selective habitat that allows some species of bacteria to grow in preference to others. The nutrients provided by the breakdown products of a necrotic pulp, tissue fluid, and serum from surrounding tissues along with low oxygen tension, and bacterial by-products support the growth of selected microorganisms (Table 1). The coronal portion of a root canal may harbor organisms different from those in the

apical portion including different strains of the same species.³⁴ When root canal walls were observed with a scanning electron microscope, patterns of colonization were not uniform even in the same specimen³⁵ (Figure 1). Clumps of bacteria were seen that appeared to be self-aggregating while other clumps had different morphologic types and appeared to be co-aggregating.³⁵ Statistical odds ratios have been used to show a relationship between certain combinations of organisms in endodontic infections but the clinical significance is unknown.^{6,7,36-41} The polymerase chain reaction (PCR), a molecular method, has been used to show that geographical differences exist among endodontic infections.²² When PCR was used to detect microbes in endodontic abscess samples from patients either in Portland, Ore., or in Rio de Janeiro, Brazil, there was a significant difference in 5 of the 8 organisms tested.²²

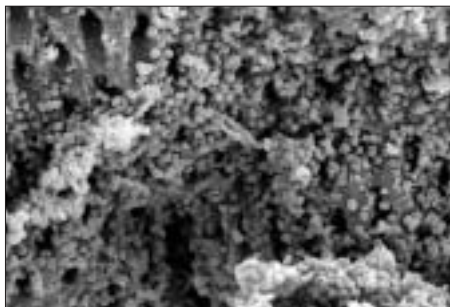


Figure 1. This scanning electron microscopic photo shows both cocci and bacilli on the surface of dentin and extending into the dentinal tubules. (Courtesy of José Siqueira.)

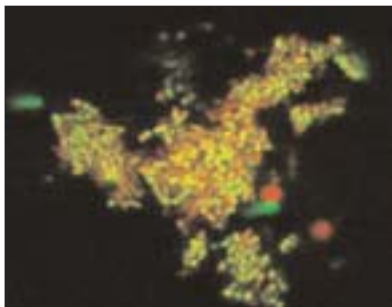


Figure 2. This confocal microscopic photo shows coaggregation of *Actinomyces* and *Eubacterium*. (Courtesy of Saengusa Kheemaeleakul.)

Table 2

NOMENCLATURE FOR PREVIOUS “*BACTEROIDES*” SPECIES

Porphyromonas – Dark-pigmented (asaccharolytic *Bacteroides* species)

- *Porphyromonas asaccharolyticus* (usually non-oral)
- *Porphyromonas gingivalis**
- *Porphyromonas endodontalis**

Prevotella – Dark-pigmented (saccharolytic *Bacteroides* species)

- *Prevotella melaninogenica*
- *Prevotella denticola*
- *Prevotella loescheii*
- *Prevotella intermedia*
- *Prevotella nigrescens**
- *Prevotella corporis*
- *Prevotella tanneriae*

Prevotella – Nonpigmented (saccharolytic *Bacteroides* species)

- *Prevotella buccae**
- *Prevotella bivia*
- *Prevotella oralis*
- *Prevotella oris*
- *Prevotella oulorum*
- *Prevotella ruminicola*

* Most commonly isolated species of black-pigmented bacteria

Coaggregation of different species of bacteria or self aggregation of the same species may provide the organisms with protection from the host's defenses and provide nutrients from the surrounding bacteria^{19,42-46} (Figure 2). The combination of *Fusobacterium nucleatum* with dark-pigmented bacteria *Prevotella intermedia* and *Porphyromonas gingivalis* has been shown to be more virulent than when the bacteria are in pure culture.⁴⁷ This supports the concept that there is a

synergistic relationship between bacteria in an endodontic infection. Numerous bacteria have been associated with various clinical signs and symptoms but no absolute correlation has been made.^{6,29,36,48-56}

Gram-negative bacteria, especially dark (black) pigmented bacteria, have received a great deal of attention. Depending on the species of dark-pigmented bacteria and the culture media, the color of the colonies may vary from

tan to black. Because of numerous taxonomic changes for dark-pigmented bacteria based on DNA studies, it is difficult to relate older studies to contemporary studies. Table 2 shows the current nomenclature of the 10 species of dark-pigmented bacteria found in humans. For example, the species *Porphyromonas endodontalis* was separated from *P. gingivalis* and *Prevotella nigrescens* was separated from *P. intermedia*.^{6,57-59} The virulence potential of dark-pigmented bacteria has been studied in animals. Strains of cultivable bacteria have been shown to have the capability to resist phagocytosis, degrade immunoglobulins, and increase pathogenesis when in combination with other specific strains of bacteria (e.g. *P. gingivalis* and *Fusobacterium nucleatum*).^{13,14,47,60} Pathogenicity may be related to the presence of lipopolysaccharide (LPS) on the outer membrane of gram-negative bacteria. LPS has been demonstrated in root canals and periradicular tissues and related to the severity of disease.^{16,18,61-63} LPS (endotoxin) is released from gram-negative bacteria during multiplication and cell death. Once released bacterial endotoxin causes a series of biological effects, which produce inflammation and periapical bone resorption.^{64,65} The cytotoxic lipid A moiety in LPS is hydrolyzed by alkaline chemicals especially calcium hydroxide.⁶⁴⁻⁶⁶

Gram-positive bacteria that are differentiated from gram-negative bacteria by a relative thick layer of peptidoglycan have also been associated with endodontic disease.^{6,29,36,48-56} *Actinomyces* may colonize periapical tissues. Aggregates of organisms may be recognized in periradicular biopsy sections as sulfur granules.^{52,67-69} Because some of the granules are yellow colored, older literature refer to them as sulfur granules.⁶⁷ The species *A. israeli* is often associated with cervical-facial actinomycosis. The cell surface of *A. israeli* has long pili believed to participate in attachment to other species of bacteria and other sur-

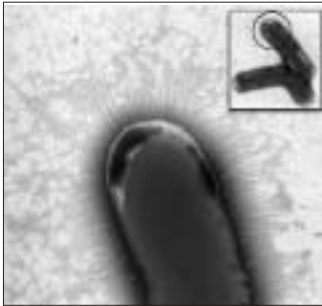


Figure 3. An electron microscopical view of hair-like fimbriae on the surface of *Actinomyces israelii*. Reproduced with permission from the Australian Dental Association, Figdor D, Davies J. Cell surface structures of *Actinomyces israelii*. *Australian Dent J* 42(2):125-8, 1997.

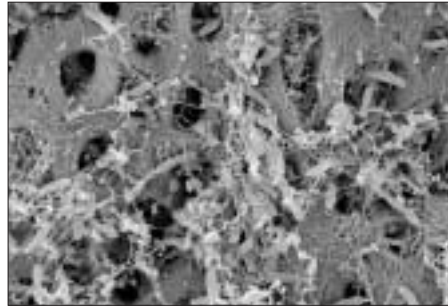


Figure 4. This scanning electron microscopical photo shows the surface of a root canal with cocci and bacilli on the surface of necrotic pre-dentin. Some organisms are in the pre-dentin openings to the dentinal tubules. The pre-dentin openings were previously occupied by the cell bodies of the odontoblasts. (Courtesy of José Siqueira.)

faces^{43,70} (Figure 3). A recent study using the PCR detected species of *Actinomyces* (*israelii*, *naeslundii*, *viscosus*) in 80 percent of the infected root canals and 46 percent of periradicular abscesses.⁷¹ The species *A. israelii* was detected in root canals 27 percent of the time and in periradicular abscesses 26 percent of the time.⁷¹ This suggests that our clinical methods of root canal debridement and surgical endodontics are successful even when *Actinomyces* is present. While cervical-facial actinomycosis may require long-term antibiotics, studies have shown that antibiotics may not be needed for endodontic infections with *Actinomyces*.^{72,73} If antibiotics are indicated because of continued clinical signs and symptoms, a short-term regimen should be adequate.^{72,73}

Other gram-positive bacteria often cultured from endodontic infections include *Peptostreptococci*, *Streptococcus*, *Enterococcus*, and *Eubacterium*.^{37,51,74,75} Using PCR, *Peptostreptococci micros* was detected in 28 percent of the infected root canals tested.⁷⁵

Spirochetes (treponemes) have been difficult to isolate in pure culture from endodontic polymicrobial infections. Recently, DNA hybridization and PCR have been used to screen for spirochetes.^{7,40,41,76-78} Using PCR, it was determined that 60 percent of samples from

abscesses/cellulitis contained spirochetes and 37 percent of asymptomatic teeth with periradicular lesions contained spirochetes.⁷ The spirochetes most commonly detected were *Treponema socranskii* (45 percent) followed by *T. maltophilum* (30 percent), *T. denticola* (29 percent), *T. pectinovorum* (14 percent), and *T. vincentii* (5 percent).⁷

Fungi have been cultivated and detected using molecular methods in infected root canal.⁷⁹⁻⁸³ When using PCR, *Candida albicans* was detected in 21 percent of infected root canals but not in any aspirates of purulence from endodontic abscesses.⁸³ Electron microscopy has detected fungi in infected root canals but not in periapical tissues.^{84,85}

Viruses may also be associated with endodontic disease. Bacteriophages are viruses that infect bacteria and carry DNA into the genome of the bacteria.^{86,87} The human immunodeficiency virus has been detected in the dental pulp and the periapex.^{151,152} Both the cytomegalovirus and Epstein-Barr virus have been associated with symptomatic endodontic infections.^{86,87} Future studies will likely show more relationships between viruses and endodontic disease.

Molecular methods such as DNA hybridization and PCR detect and identify many more microorganisms than

the so-called "gold standard" of culturing. Molecular methods are much more sensitive and offer precise identification at the DNA level. A disadvantage of molecular methods is not knowing if the DNA was from an alive or dead organism. Currently, antibiotic susceptibility tests cannot be accomplished without viable organisms. In the future, probes may be used to identify antimicrobial resistant genes in the DNA samples without having to grow the organisms for susceptibility tests.

Periradicular Endodontic Infections

Once a necrotic pulp is infected, the root canal system becomes a sanctuary for microbes (Figure 4). They often seem to be contained by a layer of neutrophils or an epithelial plug at the apical foramen.⁸⁵ Plaque-like biofilms have been observed in the foramen and root-end of an infected canal.⁸⁸ Extraradicular bacteria are usually associated with acute symptoms, the presence of a sinus tract, an infected cyst, or in cases not responding to endodontic treatment. Both acute and chronic periradicular abscesses are polymicrobial infections with large numbers of bacteria.^{29,89} With the exception of species of *Propionibacterium* and *Actinomyces*, it is controversial if asymptomatic lesions harbor extraradicular bacteria for very long beyond initial invasion of the tissue.^{52,68,90} Periapical inflammatory lesions (granulomas) contain macrophages, lymphocytes (T-cells and B-cells), plasma cells and neutrophils.⁹¹⁻⁹³ Their function is to prevent microorganisms from invading periradicular tissues. Both the pulp and periradicular inflammatory tissues have been shown to mount cellular and humoral responses to the microorganisms.⁹⁴⁻¹⁰⁰ Microbial invasion of periradicular tissues results in production of an abscess or cellulitis. Patients with an abscess or cellulitis have significant clinical signs and symptoms as a result of both nonspecific inflammation and spe-

Table 3

COMPARISON OF RETREATMENT STUDIES CULTURING *ENTEROCOCCUS FAECALIS*

Study	Molander 1998	Sundqvist 1998	Piciuliene 2000	Handcock 2001	Piciuliene 2001	Pinheiro 2003
Canals Cultured	100	54	25	54	40	60
Positive Cultures	32	24	20	34	33	51
% Gm+	85	87	nd*	80	nd	83
% Facultative	69	58	nd	56	nd	57
Species in Canal	1.7	1.3	nd	1.7	nd	1.8
Canals with <i>E. faecalis</i> 25%		16%	56%	16%	52% 4	5%

* – not determined

cific immunological responses. In studies that examined periapical inflammatory lesions microscopically, extracellular bacteria were only seen when the associated teeth were symptomatic.^{84,85,101} However, several studies using culturing methods have isolated bacteria from “asymptomatic lesions.”¹⁰²⁻¹⁰⁵ Some of the patients reported in these studies had a sinus tract (fistula) through the mucosa or the attachment apparatus. Sinus tracts are associated with chronic periradicular abscesses (suppurative apical periodontitis) that always have a polymicrobial infection. They are relatively asymptomatic because the sinus tract provides a pathway of drainage. It is possible that some specimens in these studies were contaminated with microbes from the root-end and apical foramen during curettement of the specimen. It is also possible that some samples were contaminated with salivary bacteria during the surgical procedure. Molecular methods have demonstrated the presence of microbial DNA in tissues removed during surgical treatment of asymptomatic periradicular lesions.^{106,107} Whether the microbial DNA is from viable or non-viable microbes cannot be determined and there is the possibility of sample contamination. Future studies should clarify these findings.

Invasion of periradicular tissues is related to the virulence of the microorganisms and the host’s resistance. Periapical inflammatory lesions are dynamic inflammatory events and may contain an abscess with bacteria, a cyst (possibly infected), and surrounding inflammatory tissue simultaneously at the time of sample collection.¹⁰⁸ A major reason for persistent periradicular lesions is remaining intra-radicular infection caused by an incompletely debrided root canal space.^{84,109} This concept is supported by the high success rate attained when root-ends are resected and root-end fillings are placed to seal the apical canal system of teeth with failing nonsurgical endodontics.^{110, 111}

Bacteria Isolated after Unsuccessful Endodontic Treatment

The lack of periradicular healing following root canal treatment seems most likely to be related to the persistence of microbes in the root canal system. This would seem to be related to an inability to effectively shape, clean, and seal the complete root canal system. Interestingly, the microflora cultured from previously filled root canals with persistent apical lesions differs significantly for the microbes in untreated

necrotic canals.^{24,26,109,112,113} Bacteria isolated from canals previously obturated but still associated with radiographic lesions tend to have more facultative bacteria rather than strict anaerobes.^{26,109,112-117} (Table 3). Instead of having approximately equal amounts of gram-negative and gram-positive bacteria, bacteria isolated from canals previously filled tend to have only one to two cultivable strains of mainly gram-positive bacteria. In several studies, previously filled canals had a relative increase in the presence of *Enterococcus faecalis*.^{26,109,112-117} This is likely the result of a change in selective pressures that differ in a canal filled with gutta-percha/sealer and a canal with necrotic pulp. The percentages of other species varied among the studies and there were many cases with no cultivable bacteria.

A recent study used PCR to detect the presence of bacteria in all 22 previously root-filled teeth with persistent periradicular lesions.¹¹⁸ *E. faecalis* was detected in 17/22 (77 percent) of the failing treatments. The next most detected organisms were *Propionibacterium alactolyticus* (12/22), *P. propionicum* (11/22), *Filofactor alocis* (10/22), and *Dialiste pneumosintes* (10/22).¹¹⁹ The average number of species found in each canal was four organisms compared with a mean of less than two for studies

that culture for bacteria.^{26,109,112-117} This illustrates a relative increase in sensitivity in the ability of molecular techniques to detect organisms compared to cultivation of the organisms. *Filofactor alocis* and *Dialiste pneumosintes* have not been isolated from previously filled root canals with periradicular lesions.¹¹⁹ They are anaerobic bacteria recently shown to be prevalent in untreated root canals.^{119,120} The presence of bacteria in all of the failed root canals supports the assertion that the vast majority of endodontic treatment failures are caused by intraradicular infections.

The use of calcium hydroxide in canals may contribute to the selection of *E. faecalis* in failed endodontics. A recent study demonstrated that *E. faecalis* is resistant to calcium hydroxide at a pH of 11.1 but not pH 11.5. *E. faecalis* has a proton pump that can be used to decrease the pH to the level it needs for survival.¹²¹ Another study has shown that the addition of chlorhexidine to calcium hydroxide increases the efficacy of calcium hydroxide to inhibit the growth of *E. faecalis*.¹²²

Endodontic Abscesses and Cellulitis

The extent of endodontic infections beyond the root canal system is related to the virulence of the bacteria, host response, and associated anatomy. Infections may localize or continue to spread. An abscess is a cavity of purulent exudate (pus) consisting primarily of bacteria, bacterial by-products, inflammatory cells, lysed cells and their contents. The content of inflammatory cells includes enzymes, which are damaging to the surrounding tissues. Endodontic abscesses are polymicrobial infections with organisms similar to those found in infected root canals.^{29,49,123-127}

A diffuse erythematous cellulitis results if the infection spreads into surrounding tissues. The spread of infection into deep facial spaces may be life

threatening.¹²⁸ Facial spaces are potential anatomic areas between fascia and underlying tissues and organs that provide a pathway for spread of an infection.¹²⁸ A diffuse cellulitis may have foci of purulence (abscess). The spread of infection and ensuing edema associated with inflammation often produces an indurated swelling. Over time, neutrophils accumulate and produce a fluctuant abscess. This concept supports the rationale for early incision for drainage

THE PRESENCE OF BACTERIA IN ALL OF THE FAILED ROOT CANALS SUPPORTS THE ASSERTION THAT THE VAST MAJORITY OF ENDODONTIC TREATMENT FAILURES ARE CAUSED BY INTRARADICULAR INFECTIONS.

to provide a pathway for the drainage of bacteria, bacterial by-products, and inflammatory mediators.¹²⁸ Drainage also improves circulation to the area so if antibiotics are prescribed they will more likely be delivered at a minimum inhibitory concentration.

Treatment of Acute Abscesses and Cellulitis

As with any disease process, diagnosis is of most importance. The correct diagnosis of an abscess or cellulitis of endodontic origin allows appropriate management. Chemomechanical debridement of the associated root canal system will remove the cause of the infection, however, drainage from the access opening does not significantly reduce postoperative pain or swelling.¹²⁹ Incision for drainage will usually allow rapid improvement in the patient's condition. Follow-up on a daily basis should be made to see if fur-

ther treatment is indicated.

The prescription of adjunctive antibiotics is recommended in conjunction with appropriate endodontic treatment for progressive or persistent infections with the following signs and symptoms: fever (>100° F.), malaise, cellulitis, lymphadenopathy, and unexplained trismus.¹²⁸ Antibiotics are not recommended for an irreversible pulpitis, an acute apical periodontitis, a draining sinus tract, after endodontic surgery, or incision for drainage of a localized abscess (without fever, cellulitis, or lymphadenopathy).¹³⁰⁻¹³⁴

Ideally, the choice of an antibiotic would be based on susceptibility testing of the organisms isolated from each patient's infection. Unfortunately, it takes days and sometimes weeks to culture, isolate each organism in pure culture, and do antibiotic susceptibility tests for anaerobic bacteria. Instead, recommendations based on clinical experience and previous susceptibility testing are made for normal healthy patients. It is prudent to get antibiotic susceptibility tests for immunocompromised patients if initial treatment is not successful. Patients must be made aware of benefits versus risks of taking antibiotics. Case reports have implicated antibiotics with reduction in the effectiveness of oral contraceptives; however, rifampin is the only antimicrobial shown to have such an effect.¹³⁵ Interactions of prescribed antibiotics with other medications are always of concern. For example, macrolide antibiotics should not be prescribed for a patient taking HMG-CoA reductase inhibitors such as Lipitor.

Antibiotics should be taken for two to three days after resolution of the major clinical signs and symptoms. To prevent selection of resistant organisms, a high dose of antibiotic for a short term is preferred to a low dose for a long term. A six- to seven-day around-the-clock regimen is adequate for the majority of patients once the source of the infections is removed. Recent antibiotic susceptibility



tests have shown that penicillin VK is still the antibiotic of choice for endodontic infections.^{136,137} It is prescribed with a loading dose of 1,000 mg followed by 500 mg every four to six hours. Amoxicillin has a broader spectrum and is recommended for the most serious infections. Amoxicillin in combination with clavulanate (Augmentin) is effective against beta lactamase producing organisms. Amoxicillin or amoxicillin with clavulanate is prescribed with a loading dose of 1,000 mg followed by 500 mg every eight hours. Because metronidazole is only effective against anaerobes, it should not be prescribed by itself. Metronidazole may be prescribed in combination with penicillin. It is prescribed with a loading dose of 1,000 mg followed by 500 mg every four to six hours.

For patients allergic to penicillin, clarithromycin or azithromycin may be considered instead of erythromycin. Erythromycin is not effective against the anaerobes commonly found in endodontic infections. For patients allergic to penicillin with serious infections, clindamycin is recommended. Clindamycin is prescribed with a loading dose of 600 mg and followed by 300 mg every six hours.

Metastatic Infection Associated with Endodontic Infections

Endodontic infections may be associated with metastatic infections by direct extension of the infection, via microbes carried through the blood (bacteremia), and by the release of bacterial products and inflammatory mediators. The direct extension of a periradicular abscess may reach the maxillary sinuses, cavernous sinus, orbit, brain, or via parapharyngeal pathways produce Ludwig's angina. The importance of removing the source of the infection, providing drainage, and adjunctive antimicrobial support has been discussed.

A bacteremia may be produced with both nonsurgical root canal instrumentation and surgical treatment.¹³⁸⁻¹⁴² In

normal healthy individuals, bacteremias are usually of no consequence because the immune system rapidly eliminates the microbes. Bacteremias associated with the oral cavity occur with mastication, flossing, toothbrushing, and other daily activities. Bacteremia is considered a risk factor for the development of infective endocarditis in patients with congenital or acquired cardiac defects. Although dental procedures have not been confirmed

RECENT ANTIBIOTIC SUSCEPTIBILITY TESTS HAVE SHOWN THAT PENICILLIN VK IS STILL THE ANTIBIOTIC OF CHOICE FOR ENDODONTIC INFECTIONS.

as risk factors, the American Dental Association does recommend prophylactic antibiotics for patients susceptible to infective endocarditis or with artificial prosthetic devices.¹⁴³⁻¹⁴⁵

Metastatic infections are not the same as the *Theory of Focal Infection* which still receives some attention.¹⁴⁶ Focal infection was defined as a localized or generalized infection caused by the dissemination of bacteria or their toxic products from a distant focus of infection.¹⁴⁷ In general, the support of this theory was anecdotal or flawed research.¹⁴⁸ However, recent studies suggest a relationship between the elevated values of C-reactive proteins and other inflammatory proteins that accompany chronic periodontal infections to be associated with atherosclerosis, cardiovascular, cerebrovascular disease, or preterm low-birthweight.^{149,150} Future studies must determine if these relationships are causal or consequential.

Summary

In summary, this article reviewed the microbiologic aspects of endodontic infections with an emphasis on removal of the cause of the infection. In addition, recommendations for appropriate adjunctive use of antibiotics was presented. These recommendations are based on recent antibiotic susceptibility tests. Finally, the issue of metastatic endodontic infections versus the "theory of focal infection" was presented. **CDA**

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References / 1. Leeuwenhoek A, Leeuwenhoek's letter. *Philosophical Transactions of the Royal Society of London* 14(159):568-74, 1684.

2. Miller WD, *Microorganisms of the human mouth*. Philadelphia: The S.S. White Dental Mfg. Co.; 1890.

3. Miller W, Decomposition of the contents of the dentinal tubules as a disturbing factor in the treatment of pulpless teeth. *Ohio J Dental Sc* 10:288, 1890.

4. Xia T, Baumgartner JC, David LL, Isolation and identification of *Prevotella tanneriae* from endodontic infections. *Oral Micro and Immun* 15:273-5, 1999.

5. Munson M, Pitt-Ford T, Chong B, Weightman A, Wade W, Molecular and cultural analysis of the microflora associated with endodontic infections. *J Dent Res* 81:761-6, 2002.

6. Fouad A, Barry J, Caimano M, PCR-based identification of bacteria associated with endodontic infections. *J Clin Microbiol* 40:3223-31, 2002.

7. Baumgartner JC, Khemaleelakul S, Xia T, Association of spirochetes with endodontic infections. *J Endod* 29(4):290, 2003.

8. Kakehashi S, Stanley HR, Fitzgerald RJ, The effects of surgical exposures of dental pulps in germ-free and conventional laboratory rats. *Oral Surg Oral Med Oral Pathol* 20:340-9, 1965.

9. Delivanis PD, Snowden RB, Doyle RJ, Localization of blood-borne bacteria in instrumented unfilled root canals. *Oral Surg Oral Med Oral Pathol* 52(4):430-2, 1981.

10. Delivanis PD, Fan VSC, The localization of blood-borne bacteria in instrumented unfilled and overinstrumented canals. *J Endod* 10(11):521-4, 1984.

11. Allard U, Stromberg T, Inflammatory reaction in the apical area of pulpectomized and sterile root canals in dogs. *Oral Surg Oral Med Oral Pathol* 48(5):463-6, 1979.

12. Tziafas D, Experimental bacterial anachoresis in dog dental pulps capped with calcium hydroxide. *J Endod* 15(12):591-5, 1989.

13. Sundqvist G, Bloom GD, Enberg K, Johansson E, Phagocytosis of *Bacteroides melanogenicus* and *Bacteroides gingivalis* in vitro by human neutrophils. *J Periodont Res* 17:113-21, 1982.

14. Sundqvist G, Carlsson J, Herrmann B, Tärnvik A, Degradation of human immunoglobulins G and M and complement factors C3 and C5

by black-pigmented *Bacteroides*. *J Med Microbiol* 19:85-94, 1985.

15. Sundqvist G, Carlsson J, Hånström L, Collagenolytic activity of black-pigmented *Bacteroides* species. *J Periodont Res* 22:300-6, 1987.

16. Horiba N, Maekawa Y, Abe Y, Ito M, Matsumoto T, Nakamura H, Correlations between endotoxin and clinical symptoms or radiolucent areas in infected root canals. *Oral Surg Oral Med Oral Pathol* 71(4):492-5, 1991.

17. Horiba N, Maekawa Y, Yamauchi Y, Ito M, Matsumoto T, Nakamura H, Complement activation by lipopolysaccharides purified from gram-negative bacteria isolated from infected root canals. *Oral Surg Oral Med Oral Pathol* 74(5):648-51, 1992.

18. Dwyer TG, Torabinejad M, Radiographic and histologic evaluation of the effect of endotoxin on the periapical tissues of the cat. *J Endod* 7(1):31-5, 1981.

19. Kinder SA, Holt SC, Characterization of coaggregation between *Bacteroides gingivalis* T22 and *Fusobacterium nucleatum* T18. *Infect Immun* 57:3425-33, 1989.

20. Eftimiadi C, Stashenko P, Tonetti M, Mangiante PE, Massara R, Zupo S, et al. Divergent effect of the anaerobic bacteria by-product butyric acid on the immune response: suppression of T-lymphocyte proliferation and stimulation of interleukin-1 beta production. *Oral Microbiol Immunol* 6:17-23, 1991.

21. Maita E, Horiuchi H, Polyamine analysis of infected root canal contents related to clinical symptoms. *Endod Dent Traumatol* 6(5):213-7, 1990.

22. Baumgartner JC, Sequeira JJ, Xia T, Rocas I, Geographical differences in bacteria detected in endodontic infections using PCR. *J Endod* 28:238, 2002.

23. Kobayashi T, Hayashi A, Yoshikawa R, Okuda K, Hara K, The microbial flora from root canals and periodontal pockets of non-vital teeth associated with advanced periodontitis. *Int Endod J* 23:100-6, 1990.

24. Rolph H, Lennon A, Riggio M, Molecular identification of microorganisms from endodontic infections. *J Clin Microbiol* 39:3282-9, 2001.

25. Siqueira JF Jr, Taxonomic changes of bacteria associated with endodontic infections. *J Endod* 29(10):619-23, 2003.

26. Möller ÅJR, Microbiological examination of root canals and periapical tissues of human teeth. *Odontol Tidskr* 74(1), 1966.

27. Bergenholtz G, Micro-organisms from necrotic pulp of traumatized teeth. *Odont Revy* 25(4):347-58, 1974.

28. Sundqvist GK. Bacteriological studies of necrotic dental pulps [Odontological Dissertation No. 7]: University of Umea: Umea, Sweden; 1976.

29. Van Winkelhoff AJ, Carlee AW, de Graaff J, *Bacteroides endodontalis* and other black-pigmented *Bacteroides* species in odontogenic abscesses. *Infect Immun* 49:494-7, 1985.

30. Baumgartner JC, Falkler Jr WA, Bacteria in the apical 5 mm of infected root canals. *J Endod* 1991;17(8):380-3.

31. Möller ÅJR, Fabricius L, Dahlén G, Öhman AE, Heyden G. Influence on periapical tissues of indigenous oral bacteria and necrotic pulp tissue in monkeys. *Scand J Dent Res* 89:475-84, 1981.

32. Fabricius L, Dahlén G, Öhman AE, Möller ÅJR, Predominant indigenous oral bacteria isolated from infected root canals after varied times of closure. *Scand J Dent Res* 90:134-44, 1982.

33. Fabricius L, Dahlén G, Holm SE, Möller ÅJR, Influence of combinations of oral bacteria on periapical tissues of monkeys. *Scand J Dent Res* 90:200-6, 1982.

34. Dougherty W, Bae K, Watkins B, Baumgartner J, Black-pigmented bacteria in coronal and apical segments of infected root canals. *J Endod* 24(5):356-8, 1998.

35. Siqueira JF Jr, Rocas I, Lopes H, Patterns of microbial colonization in primary root canal infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 93(2):174-88, 2002.

36. Gomes B, Drucker D, Lilley J, Positive and negative associations between bacterial species in dental root canals. *Microbios* 80(325):231-43, 1994.

37. Gomes B, Lilley J, Drucker D, Associations of endodontic symptoms and signs with particular combinations of specific bacteria. *Int Endod J* 29:69-75, 1996.

38. Sundqvist G, Associations between microbial species in dental root canal infections. *Oral Microbiol Immunol* 7:257-62, 1992.

39. Peters L, Wesselink PR, van Winkelhoff A-J, Combinations of bacterial species in endodontic infections. *Int Endod J* 35:698-702, 2002.

40. Jung I-Y, Choi B-k, Kum K-Y, Yoo Y-J, Yoon T-C, Lee S-J, et al. Identification of oral spirochetes at the species level and their association with other bacteria in endodontic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 92:329-34, 2001.

41. Jung I-Y, Choi B-K, Kum K-Y, Roh B-D, Lee S-J, Lee C-Y, et al. Molecular epidemiology and association of putative pathogens in root canal infection. *J Endod* 26(10):599-604, 2004.

42. Kolenbrander PE, Andersen RN, Inhibition of coaggregation between *Fusobacterium nucleatum* and *Porphyromonas (Bacteroides) gingivalis* by lactose and related sugars. *Infect Immun* 57:3204-9, 1989.

43. Nesbitt W, Fukushima H, Leung K-P, Clark W, Coaggregation of *Prevotella intermedia* with oral actinomyces species. *Infect Immun* 61(5):2011-4, 1993.

44. Grimaudo NJ, Nesbitt WE, Coaggregation of *Candida albicans* with oral *Fusobacterium* species. *Oral Microbiol Immunol* 12:168-73, 1997.

45. Noiri Y, Ehara A, Kawahara T, Takemura N, Ebisu S, Participation of bacterial biofilms in refractory and chronic periapical periodontitis. *J Endod* 28(10):679-83, 2002.

46. Khemaleelakul S, Baumgartner JC, Pruksakorn S, Coaggregation of bacteria associated with acute endodontic infections. *J Endod* in press 2004.

47. Baumgartner JC, Falkler WA, Beckerman T, Experimentally induced infection by oral anaerobic microorganisms in a mouse model. *Oral Microbiol Immunol* 7:253-6, 1992.

48. Sundqvist G, Johansson E, Sjögren U, Prevalence of black-pigmented *Bacteroides* species in root canal infections. *J Endod* 15:13-9, 1989.

49. Baumgartner JC, Watkins BJ, Prevalence of black-pigmented bacteria associated with root canal infections. *J Endod* 20(4):191, 1994.

50. Griffie MB, Patterson SS, Miller CH, Kafrawy AH, Newton CW, The relationship of *Bacteroides melaninogenicus* to symptoms associated with pulpal necrosis. *Oral Surg Oral Med Oral Pathol* 50(5):457-61, 1980.

51. Yoshida M, Fukushima H, Yamamoto K, Ogawa K, Toda T, Sagawa H, Correlation between clinical symptoms and microorganisms isolated from root canals of teeth with periapical pathosis. *J Endod* 13(1):24-8, 1987.

52. Happonen RP, Periapical actinomycosis: a follow-up study of 16 surgically treated cases. *Endod Dent Traumatol* 2:205-9, 1986.

53. Hashioka K, Suzuki K, Yoshida T, Nakane A, Horiba N, Nakamura H, Relationship between clinical symptoms and enzyme-producing bacteria isolated from infected root canal. *J Endod* 20(2):75-

7, 1994.

54. Heimdahl A, Von Konow L, Satoh T, Nord CE, Clinical appearance of orofacial infections of odontogenic origin in relation to microbiological findings. *J Clin Microbiol* 22:299-302, 1985.

55. Brook I, Frazier EH, Gher ME, Microbiology of periapical abscesses and associated maxillary sinusitis. *J Periodontol* 67(6):608-10, 1996.

56. Haapasalo M, Ranta H, Ranta K, Shah H, Black-pigmented *Bacteroides* spp. in human apical periodontitis. *Infect Immun* 53:149-53, 1986.

57. Gharbia S, Haapasalo M, Shah H, Kotiranta A, Lounatmaa K, Pearce M, et al. Characterization of *Prevotella intermedia* and *Prevotella nigrescens* isolates from periodontic and endodontic infections. *J Periodontol* 65(1):56-61, 1994.

58. Van Steenberghe TJM, Van Winkelhoff AJ, Mayrand D, Grenier D, De Graaff J, *Bacteroides endodontalis* sp. nov., an asaccharolytic black-pigmented *Bacteroides* species from infected dental root canals. *Int J Syst Bacteriol* 34:118-20, 1984.

59. Baumgartner J, Bae K, Xia T, Whitt J, David L, Sodium dodecyl sulfate-polyacrylamide gel electrophoresis and polymerase chain reaction for differentiation of *Prevotella intermedia* and *Prevotella nigrescens*. *J Endod* 25(5):324-8, 1999.

60. Sundqvist GK, Carlsson J, Herrmann BF, Höfling JF, Väättäinän A, Degradation in vivo of the C3 protein of guinea-pig complement by a pathogenic strain of *Bacteroides gingivalis*. *Scand J Dent Res* 92:14-24, 1984.

61. Schein B, Schilder H, Endotoxin content in endodontically involved teeth. *J Endod* 1(1):19-21, 1975.

62. Schonfeld S, Greening A, Glick D, Frank A, Simon J, Endotoxic activity in periapical lesions. *Oral Surg Oral Med Oral Pathol* 53(1):82-7, 1982.

63. Horiba N, Maekawa Y, Matsumoto T, Nakamura H, A study of the distribution of endotoxin in the dentinal wall of infected root canals. *J Endod* 16(7):331-4, 1990.

64. Nelson-Filho P, Leonardo MR, Silva LAB, Assed S, Radiographic evaluation of the effect of endotoxin (OPS) plus calcium hydroxide on apical and periapical tissues of dogs. *J Endod* 28(10):694-6, 2002.

65. Yamasaki M, Nakane A, Kumazawa M, Hashioka K, Horiba N, Nakamura H, Endotoxin and gram-negative bacteria in the rat periapical lesions. *J Endod* 18(10):501-4, 1992.

66. Safavi KE, Nichols FC, Effect of calcium hydroxide on bacterial lipopolysaccharide. *J Endod* 19(2):76-8, 1993.

67. Sunde P, Olsen I, Debelian G, Tronstad L, Microbiota of periapical lesions refractory to endodontic therapy. *J Endod* 28(4):304-10, 2002.

68. Sundqvist G, Reuterving CO, Isolation of *Actinomyces israelii* from periapical lesion. *J Endod* 6:602-5 1980.

69. Siqueira JF Jr, Rocas I, Souto R, de Uzeda M, Colombo A, Actinomyces species, streptococci, and enterococcus faecalis in primary root canal infections. *J Endod* 28(3):168-72, 2002.

70. Figdor D, Davies J, Cell surface structures of *Actinomyces israelii*. *Australian Dent J* 42(2):125-8, 1997.

71. Xia T, Baumgartner JC, Occurrence of actinomyces in infections of endodontic origin. *J Endod* 29(9):549-52, 2003.

72. Rush J, Sulte H, Cohen D, Makkaway H, Course of infection and case outcome in individuals diagnosed with microbial colonies morphologically consistent with actinomyces species. *J Endod* 28(8):613-8, 2002.

73. Barnard D, Davies J, Figdor D, Susceptibility of *Actinomyces israelii* to antibiotics,

sodium hypochlorite and calcium hydroxide. *Int Endod J* 29:320-6, 1996.

74. Gomes BPFA, Drucker DB, Lilley JD, Association of specific bacteria with some endodontic signs and symptoms. *Int Endod J* 27(6):291-8, 1994.

75. Siqueira JF Jr, Rocas I, Andrade A, de Uzeda M, Peptostreptococcus micros in primary endodontic infections as detected by 16S rDNA-based polymerase chain reaction. *J Endod* 29(2):111-3, 2003.

76. Rôças I, Siqueira JF Jr, Andrade A, Uzeda M, Oral treponemes in primary root canal infections as detected by nested PCR. *Int Endod J* 36:20-6, 2003.

77. Alapati S, Brantley W, Svec T, Powers J, Mitchell J, Scanning electron microscope observations of new and used nickel-titanium rotary files. *J Endod* 29(10):667-9, 2003.

78. Siqueira JF Jr, Rôças JN, Souto R, de Uzeda M, Colombo AP, Checkerboard DNS-DNA hybridization analysis of endodontic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 89(6):744-8, 2000.

79. Sen B, Safavi K, Spangberg L, Growth patterns of candida albicans in relation to radicular dentin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 84(1):68-73, 1997.

80. Sen BH, Piskin B, Demirci T, Observation of bacteria and fungi in infected root canals and dentinal tubules by SEM. *Endod Dent Traumatol* 11(1):6-9, 1995

81. Waltimo TMT, Sirén EK, Torkko HLK, Olsen I, Haapasalo MPP, Fungi in therapy-resistant apical periodontitis. *Int Endod J* 30:96-101, 1997.

82. Siqueira JF Jr, Rocas I, Lopes H, Elias C, de Uzeda M, Fungal infection of the radicular dentin. *J Endod* 28(11):770-3, 2002.

83. Baumgartner JC, Watts CM, Xia T, Occurrence of candida albicans in infections of endodontic origin. *J Endod* 26(12):695-8, 2000.

84. Nair PNR, Sjogren U, Krey G, Kahnberg KE, Sundqvist G, Intraradicular bacteria and fungi in root-filled, asymptomatic human teeth with therapy-resistant periapical lesions: a long-term light and electron microscopic follow-up study. *J Endod* 16(12):580-7, 1990.

85. Nair PNR, Light and electron microscopic studies of root canal flora and periapical lesions. *J Endod* 13:29-39, 1987.

86. Sabeti M, Simon J, Nowzari H, Slots J, Cytomegalovirus and Epstein-Barr virus active infection in periapical lesions of teeth with intact crowns. *J Endod* 29(5):321-3, 2003.

87. Sabeti M, Valles Y, Nowzari H, Simon J, Kermani-Arab V, Slots J, Cytomegalovirus and Epstein-Barr virus DNA transcription in endodontic symptomatic lesions. *Oral Microbiol Immunol* 18:104-8, 2003.

88. Tronstad L, Barnett F, Cervone F, Periapical bacterial plaque in teeth refractory to endodontic treatment. *Endod Dent Traumatol* 6:73-7, 1990.

89. Weiger R, Manncke B, Werner H, Lost C, Microbial flora of sinus tracts and root canals of non-vital teeth. *Endod Dent Traumatol* 11(1):15-9, 1995.

90. O'Grady JF, Reade PC, Periapical actinomycosis involving *Actinomyces israelii*. *J Endod* 14:147-9, 1988.

91. Barkhordar RA, Desousa YG, Human T-lymphocyte subpopulations in periapical lesions. *Oral Surg Oral Med Oral Pathol* 65(6):763-6, 1988.

92. Stashenko P, Wang SM, T helper and T suppressor cell reversal during the development of

induced rat periapical lesions. *J Dent Res* 68:830-4, 1989.

93. Stern MH, Dreizen S, Mackler BF, Selbst AG, Levy BM, Quantitative analysis of cellular composition of human periapical granuloma. *J Endod* 7:117-22, 1981.

94. Hahn C, Falkler WAJ, Antibodies in normal and diseased pulps reactive with microorganisms isolated from deep caries. *J Endod* 18(1):28-31, 1992.

95. Jontell M, Bergenholtz G, Scheynius A, Ambrose W, Dendritic cells and macrophages expressing Class II antigens in the normal rat incisor pulp. *J Dent Res* 67:1263-6, 1988.

96. Jontell M, Okiji T, Dahlgren U, Bergenholtz G, Immune defense mechanisms of the dental pulp. *Crit Rev Oral Biol Med* 9(2):179-200, 1998.

97. Baumgartner JC, Falkler WAJ, Reactivity of IgG from explant cultures of periapical lesions with implicated microorganisms. *J Endod* 17(5):207-12, 1991.

98. Baumgartner JC, Falkler WAJ, Biosynthesis of IgG in periapical lesion explant cultures. *J Endod* 17(4):143-6, 1991.

99. Kettering JD, Torabinejad M, Jones SL, Specificity of antibodies present in human periapical lesions. *J Endod* 17(5):213-6, 1991.

100. Kuo M, Lamster I, Hasselgren G, Host Mediators in endodontic exudates. *J Endod* 24(9):598-603, 1998

101. Walton RE, Ardjmand K, Histological evaluation of the presence of bacteria in induced periapical lesions in monkeys. *J Endod* 18(5):216-21, 1992.

102. Tronstad L, Barnett F, Riso K, Slots J, Extraradicular endodontic infections. *Endod Dent Traumatol* 3(2):86-90, 1987.

103. Wayman BE, Murata SM, Almeida RJ, Fowler CB, A bacteriological and histological evaluation of 58 periapical lesions. *J Endod* 18(4):152-5, 1992.

104. Iwu C, MacFarlane TW, MacKenzie D, Stenhouse D, The microbiology of periapical granulomas. *Oral Surg Oral Med Oral Pathol* 69:502-5, 1990.

105. Abou-Rass M, Bogen G, Microorganisms in closed periapical lesions. *Int Endod J* 31(31):39-47, 1998.

106. Sunde P, Tronstad L, Eribe E, Lind P, Olsen I, Assessment of periradicular microbiota by DNA-DNA hybridization. *Endod Dent Traumatol* 16:191-6, 2000.

107. Gatti J, Dobrik J, Smith C, White R, Socransky S, Skobe Z, Bacteria of asymptomatic periradicular endodontic lesions identified by DNA-DNA hybridization. *Endod Dent Traumatol* 16:197-204, 2000.

108. Baumgartner JC, Picket AB, Muller JT, Microscopic examination of oral sinus tracts and their associated periapical lesions. *J Endod* 10(4):146-52, 1984.

109. Sundqvist G, Figdor D, Persson S, Sjogren U, Microbiologic analysis of teeth with failed endodontic treatment and the outcome of conservative retreatment. Microbiologic analysis of teeth with failed endodontic treatment and the outcome of conservative retreatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 85(1):86-92, 1998.

110. Rubinstein R, Kim S, Short-term observation of results of endodontic surgery with the use of a surgical operation microscope and super-EBA as root-end filling material. *J Endod* 25(1):43-8, 1999.

111. Rubinstein R, Kim S, Long-term follow-

up of cases considered healed one year after apical microsurgery. *J Endod* 28(5):378-83, 2002.

112. Molander A, Reit C, Dahlen G, Kvist T, Microbiological status of root-filled teeth with apical periodontitis. *Int Endod J* 31:1-7, 1998.

113. Hancock HI, Sigurdsson A, Trope M, Moiseiwitsch J, Bacteria isolated after unsuccessful endodontic treatment in a North American population. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 91(5):579-86, 2001.

114. Siren E, Haapasalo M, Ranta K, Salmi P, Kerosuo N, Microbiological findings and clinical treatment procedures in endodontic cases selected for microbiological investigation. *Int Endo J* 30(2):91-5, 1997.

115. Peculiene V, Balciuniene I, Eriksen H, Haapasalo M, Isolation of enterococcus faecalis in previously root-filled canals in a Lithuanian population. *J Endod* 26(10):593-5, 2000.

116. Peculiene V, Reynaud A, Balciuniene I, Haapasalo M, Isolation of yeasts and enteric bacteria in root-filled teeth with chronic apical periodontitis. *Int Endod J* 34:429-34, 2001.

117. Pinheiro E, Gomes B, Ferraz C, Sousa E, Teixeira F, Souza-Filho FJ, Microorganisms from canals of root-filled teeth with periapical lesions. *Int Endod J* 36:1-11, 2003.

118. Siqueira JF Jr, Rocas I, Polymerase chain reaction-based analysis of microorganisms associated with failed endodontic treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 97(1):85-94, 2004.

119. Siqueira JF Jr, Rocas I, Detection of Filifactor alovis in endodontic infections associated with different forms of periradicular diseases. *Oral Microbiol Immunol* 18:263-5, 2003.

120. Rôças I, Sequeira JJ, Identification of Dialister pneumosintes in acute periradicular abscesses of humans by nested PCR. *Anaerobe* 8:75-8, 2002.

121. Evans M, Davies J, Sundqvist G, Figdor D, Mechanisms involved in the resistance of enterococcus faecalis to calcium hydroxide. *Int Endod J* 35:221-8, 2002.

122. Evans M, Baumgartner JC, Khemalelakul S, Xia T, Efficacy of calcium hydroxide: chlorhexidine paste as an intracanal medication in bovine dentin. *J Endod* 29(5):338-9, 2003.

123. Brook I, Frazier E, Gher MJ, Microbiology of periapical abscesses and associated maxillary sinusitis. *J Periodontol* 67(6):608-10, 1996.

124. Lewis MAO, MacFarlane TW, McGowan DA, Quantitative bacteriology of acute dento-alveolar abscesses. *J Med Microbiol* 21:101-4, 1986.

125. Williams BL, Bacteriology of dental abscesses of endodontic origin. *J Clin Microbiol* 18(4):770-4, 1983.

126. Oguntebi B, Slee AM, Tanzer JM, Langeland K, Predominant microflora associated with human dental periapical abscesses. *J Clin Microbiol* 15:964-6, 1982.

127. Baumgartner JC, Watkins JB, Bae KS, Xia T, Association of black-pigmented bacteria with endodontic infections. *J Endod* 25(6):413-5, 1999.

128. Baumgartner JC, Hutter JW, Endodontic Microbiology and Treatment of Infections. In: Cohen S, Burns R, editors. Pathways of the Pulp. 8th ed. St. Louis: C.V. Mosby; 2001.

129. Nusstein J, Reader A, Beck M, Effect of drainage upon access on postoperative endodontic pain and swelling in symptomatic necrotic teeth. *J Endod* 28(8):584-8, 2002.

130. Nagle D, Reader A, Beck M, Weaver J, Effect of systemic penicillin on pain in untreated

irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 90:636-40, 2000.

131. Pickenpaugh L, Reader A, Beck M, Meyers W, Peterson L. Effect of Prophylactic amoxicillin on endodontic flare-up in asymptomatic, necrotic teeth. *J Endod* 27(1):53-6, 2001.

132. Walton RE, Chiappinelli J, Prophylactic

penicillin: effect on post-treatment symptoms following root canal treatment of asymptomatic periapical pathosis. *J Endod* 19(9):466-70, 1993.

133. Henry M, Reader A, Beck M. Effect of penicillin on postoperative endodontic pain and swelling in symptomatic necrotic teeth. *J Endod* 27(2):117-23, 2001.

134. Fouad A, Rivera E, Walton R. Penicillin as a supplement in resolving the localized acute apical abscess. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 81(5):590-5, 1996.

135. Hersh EV. Adverse drug interactions in dental practice. *J Am Dent Assoc* 130(2):236-51, 1999.

136. Khemaleelakul S, Baumgartner JC, Pruksakorn S. Identification of bacteria in acute endodontic infections and their antimicrobial susceptibility. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 94(6):746-55, 2002.

137. Baumgartner JC, Xia T. Antibiotic susceptibility of bacteria associated with endodontic abscesses. *J Endod* 29(1):44-7, 2003.

138. Heimdahl A, Hall G, Hedberg M, Sandberg H. Detection and quantitation by lysis-filtration of bacteremia after different oral surgical procedures. *J Clin Microbiol* 28(10):2205-9, 1990.

139. Bender IB, Seltzer S, Yermish M. The incidence of bacteremia in endodontic manipulation. *Oral Surg Oral Med Oral Pathol* 13(3):353-60, 1960.

140. Baumgartner JC, Hegggers J, Harrison J. The incidence of bacteremias related to endodontic procedures. I. Nonsurgical endodontics. *J Endod* 2:135-40, 1976.

141. Baumgartner JC, Hegggers JP, Harrison JW. Incidence of bacteremias related to endodontic procedures. II. Surgical endodontics. *J Endod* 3(10):399-404, 1977.

142. Debelian GF, Olsen I, Tronstad L. Bacteremia in conjunction with endodontic therapy. *Endod Dent Traumatol* 11(3):142-9, 1995.

143. ADA, Council on Scientific Affairs: Antibiotics use in dentistry. *J Am Dent Assoc* 128(5):648, 1997.

144. ADA. Antibiotic prophylaxis for dental patients with total joint replacements. *J Am Dent Assoc* 128:1004-7, 1997.

145. Strom B, Abrutyn E, Berlin J, Kinman J, Feldman R, Stolley P, et al. Dental and cardiac risk factors for infective endocarditis: A population-based, case-control study. *Ann Intern Med* 129(10):761-9, 1998.

146. Grossman LI. Focal infection: are oral foci of infection related to systemic disease? *DCNA* 4:749, 1960.

147. Rosenow EC. The relation of dental infection to systemic disease. *Dental Cosmos* 59:485, 1917.

148. Cohen S, Burns R. *Pathways of the Pulp*. St. Louis: C.V. Mosby; 2001.

149. Williams R, Offenbacher S. Periodontal medicine: the emergence of a new branch of periodontology. *Periodontol* 23:9-12, 2000.

150. Mendall M, Patel P, Ballam L, Strachan D, Northfield T. Reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *Br Med J* 312:1061-5, 1996.

151. Glick M, Trope M, Pliskin ME. Detection of HIV in the dental pulp of a patient with AIDS. *J Am Dent Assoc* 119(5):649-50, 1989.

152. Glick M, Trope M, Bagsara, O, Pliskin ME. Human immunodeficiency virus infection of fibroblasts of dental pulp in seropositive patients. *Oral Surg Oral Med Oral Pathol* 71(6):733-6, 1991.