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Antibiotics in endodontics - A concise review

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Abstract

Bacteria have been main causative factor in the pathogenesis and progression of pulp and periapical diseases. The primary aim of endodontic treatment is to remove as many bacteria as possible from the root canal system and then to establish an environment in which remaining organisms cannot live. This can be achieved by combination of local and systemic use of antibiotics. During endodontic treatment, antibiotics may be given systemically or regionally to achieve aseptic environment. This paper elaborates on antibiotic use in the field of Endodontics.

Keywords: Endodontic infections, antibiotics, TAP, MTAD, systemic use, antibiotic prophylaxis

Introduction

In the Oral cavity over 700 species of micro organisms belonging to 11 divisions have been identified. In essence endodontic infection is the infection of root canal system and micro organisms play a tremendous role in pulpal and periapical disease. The bacteria associated with primary endodontic infection are mixed, but are predominantly gram negative anaerobic rods, where as the bacteria associated with secondary infection comprise only one or few bacterial species – most important of which is *E. Faecalis* [1].

The ultimate goal of endodontic treatment is to remove as many micro-organisms and their by-products from the root canal space by using various antimicrobial agents to provide a environment free of micro-organisms [2]. Antibiotics have revolutionized the entire health care system including both medicine and dentistry. The paradigm shift occurred since the discovery of Penicillin by Alexander Fleming in 1928 [3]. During Endodontic procedure antibiotics can be given either systemically or locally. Systemic Antibiotics should be prescribed or used for dental infections on the basis of defined indications [4]. The local application of antibiotics is an effective mode of disinfection in endodontics because systemic antibiotics fail to reach the necrotic pulp [5].

History

Mixtures with antimicrobial properties used in the treatment of infections were described over 2000 years ago [6]. Physician Paul Ehrlich laid down the foundation of antibiotics by introducing the term “magic bullets” for the agents that would adhere itself to the micro-organism and lyse it [7]. The term antibiosis was first described by Louis Pasteur and Robert Koch [8].

Local use in Endodontics

Antibiotics can be used in various modalities in endodontics. First local use of Antibiotics in endodontics was by Grossman - Father of Endodontics. In 1951 he proposed (PBSC) Poly antibiotic paste – combination of penicillin, bacitracin, streptomycin and caprylate sodium suspended in silicon vehicle [9]. Later in 1975 Food and Drug Administration banned PBSC for endodontic use, because of the risk of sensitisation and allergic reactions [10].

Table 1: Uses of Antibiotics in Endodontics

Local Uses	Systemic Uses
1. Pulp capping, 2. Irrigant, 3. Intra Canal medicament, 4. Obturating material containing antibiotics, 5. Reimplantation, 6. Regenerative endodontics	1. Signs of systemic involvement, 2. Immuno-suppressed patients, 3. Bacterimia

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Locally used antibiotic agents in endodontics (Table - 2)

1. TAP - Triple Antibiotic Paste
2. MTAD
3. Tetraclean
4. Ledermix Paste
5. Odontopaste
6. Pulpomixine
7. Septomixine Forte
8. Medicated Gutta Percha
9. Scaffolds Containing Antibiotics

Table 2: Locally used Antibiotics in Endodontics

Antibiotics in Endodontics	Uses
Triple antibiotic paste	Intracanal medicament, Regenerative endodontics
MTAD	Irrigant
Tetraclean	Irrigant
Ledermix paste	Pulp capping and intracanal medicament
Odontopaste	Intracanal medicament
Pulpomixine	Pulp capping
Septomixine forte	Intracanal medicament
Medicated gutta percha	Iodoform and tetracycline impregnated GP, Recent- nanosilver and nanodiamond coated Gutta percha

Advantages of locally used antibiotic agents

- Efficient and predictable disinfection
- A high drug concentration at the local site
- Reducing systemic complications of antibiotic medication.

Disadvantage

- Possible development of bacterial resistant strains (antimicrobial resistance)
- Allergic reactions
- Inhibition of angiogenesis
- Tooth staining or discoloration.^[11]

TAP –Triple antibiotic paste

Triple antibiotic paste is a combination of three antibiotics minocycline, ciprofloxacin and Metronidazole. Since root canal infections are poly microbial in nature and because of the complexity of infections, a combination of antibiotics is needed to address the diverse microbial flora. This combination was first used by Sato *et al.*, now commercially available as 3-MIX.MP^[12].

Metronidazole is a nitro imidazole compound; selectively toxic and effective against anaerobic organisms. Presence of redox protein reduces the nitro groups of this compound and generates free radicals that cause DNA damage and lysis of cell. Minocycline primarily bacteriostatic, inhibits protein synthesis by binding to 30S ribosome in susceptible organisms. Ciprofloxacin is a synthetic Fluoroquinolone with rapid bactericidal action. It inhibits the enzyme bacterial DNA gyrase^[13]. Sterile environment is needed for success of regeneration endodontic procedure. This TAP has been employed under the concept of “Lesion sterilization and tissue repair therapy” for treating immature teeth with endodontic infection^[14].

The effectiveness of this TAP was evaluated and studied by Hoshino *et al.*, who evaluated the antibacterial effectiveness of drugs alone as well as in combination. He finally demonstrated none of the antibiotics were able to completely remove the pathogens but the combination showed consistent

sterilisation. Hoshino *et al.* recommended metronidazole (500 mg) minocycline (100mg) and ciprofloxacin (200mg) at 1:1:1 ratio for 3mix formulation. The carrier is propylene glycol and macrogol ointment at 1:1 ratio^[15]. This formulation was later modified by Takushige *et al.* as metronidazole, minocycline and ciprofloxacin mixed in a ratio of 3:3:1^[16]. Even though TAP is effective medicament, it has its own drawback. TAP paste is shown to be most cytotoxic to human periodontal ligament fibroblasts. It causes exacerbated inflammatory reaction in subcutaneous connective tissue, and minocycline component causes discoloration. TAP is radiolucent, the vehicle propylene glycol is difficult to remove from the dentin surface and may require additional appointment and increased chance of contamination^[17].

MTAD

It is a mixture of 3% doxycycline, citric acid and a detergent polysorbate 80. MTAD is able to remove the smear layer without affecting or altering the structure of a dentinal tubules^[18, 19]. Study by Newberry *et al.* demonstrated the antimicrobial efficacy of MTAD against 8 strains of *E. Faecalis*. Here MTAD was used as a final rinse for 5 mins after irrigating the canals initially with 1.3% Naocl. This showed complete elimination of 7 out of 8 strains of bacteria^[20].

Tong *et al.* showed by adding nisin to MTAD, it enhanced its effectiveness against *E. Faecalis* biofilm^[21]. MTAD is commercially available as powder-Liquid system. Part-A is a liquid that contains 4.25% citric acid and 0.5% polysorbate 80 (Tween 80). Part B, powder contains 3% doxycycline hyclate and is a broad spectrum antibiotic. The bacteriostatic property of doxycycline is advantageous, because in the absence of bacterial cell lysis, there will be no endotoxin release and substantivity of doxycycline provides a prolonged antibacterial effect^[22]. Davis *et al.* in his in vitro study showed that 2% chlorhexidine and 5.25% naocl both exhibited less antimicrobial effectiveness against *E. Faecalis* than Biopure MTAD^[23].

Tetraclean

Tetraclean is a mixture of an antibiotic, acid and detergent, but it differs from MTAD by the concentration of doxycycline (50mg/ml) and the type of detergent polypropylene glycol^[24]. Tetraclean is more effective than MTAD against the endodontic pathogen *E. Faecalis* in the planktonic culture and mixed species in invitro biofilm^[25]. Giardino *et al.* also proved that tetraclean resulted in a high degree of bio film disintegration on nitrate membrane filters when compared with MTAD and 5.25% Naocl^[26].

Odontopaste

Odontopaste is a zinc-oxide based root canal paste with clindamycin hydrochloride 5% and 1% triamcinolone acetonide formulated and developed in Australia [Australian Dental Manufacturing, Kenmore Hills, Old Australia]. It is bacteriostatic and prevents bacterial repopulation in the root canal system. Steroid reduced the post operative pain and inflammation^[27]. There are recommendations for mixing ledermix or odontopaste with calcium hydroxide. Ledermix and calcium hydroxide can be mixed 50:50 or can be used as a separate subsequent dressing or as a medicament in the root canal system^[28].

Odontopaste itself contains 0.5% calcium hydroxide in it, hence mixing of an additional calcium hydroxide in 50:50 ratio with odontopaste is not recommended because it result

in rapid loss or destruction of steroid component in it. 0.5% is sufficient for preservation of steroid component and destruction was higher in ledermix - calcium hydroxide mixture than odontopaste - calcium hydroxide mixture. There is no real advantages of mixing calcium hydroxide with ledermix or odontopaste. There is no significant improvement in antibacterial action in the calcium hydroxide combination or mixture when compared to calcium hydroxide alone [29].

Ledermix paste

Ledermix is used both as pulp capping agent and as an intracanal medicament. Ledermix paste is a combination of 3.2% demeclocycline HCl and a steroid 1% tramcinolone acetamide in polyethylene glycol base. Steroids mainly reduce the inflammation and pain, while the antibiotics limit the infection by the microbes [30]. A modification of the paste system is available in cement form consisting of 0.7% triamcinolone, 3% demeclocycline and calcium salts, used for pulp capping, pulpotomy procedure and also as a liner for hypersensitive dentin [31].

Study by Bryson *et al.* showed that Ledermix paste plays a significant role in treatment of traumatically injured teeth. In this study ledermix medicament was placed in the canals of replanted dog teeth after a drying period of 60 minutes. Teeth treated with ledermix paste showed favourable healing and less root resorption when compared to the teeth treated with calcium hydroxide as a intra canal medicament [32]. Study by Thong *et al.*, showed the incidence of replacement resorption was significantly lower in the teeth treated with ledermix paste, when compared with calcium treated teeth [33].

Chen *et al.* stated that the steroid and tetracycline lower the inflammatory response along with inhibition of clastic cell mediated resorption and also promoting periodontal healing in replanted teeth [34]. One advantage of ledermix, paste is, it is water soluble, well rinsed out easily and does not cause systemic side effect in intradental use [35]. Kim *et al.* studied the discoloration caused by ledermix paste when used as an intracanal medicament and found this is mainly because of the presence of tetracycline in the formulation. It was suggested that if the paste is placed in the canal below the CEJ, it reduced the staining effects [36].

Medicated Gutta percha

Howard Martin introduced medicated gutta percha containing 10% Iodoform and 10% tetracycline impregnated gutta percha (TGP) intended to reduce the growth of bacteria inside the obturated root canal. TGP prevent the colonization of bacteria on the gutta percha points and within the root canals [37].

Systemic Medication

Root canal infections are polymicrobial infections characterized by anaerobic bacteria predominantly facultative anaerobes. These bacteria result in pulpal necrosis, which become reservoir of infection, that contains dead microbes and its products that reach peri-radicular region, that result in peri-radicular inflammation, leading to abscess and cellulitis. In such cases along with local use, systemic indication of antibiotics is eventually needed [38].

Responsible use of antibiotics in endodontics is a need to aid in the host defense in the elimination of the bacteria. Initially narrow spectrum of antibiotics should be the choice because, use of broad spectrum result in development of resistance. Systemic indication of antibiotics is indicated when there is a spread of infection such as fever, cellulitis, lymphadenopathy and swelling. Other indications for the use of antibiotics

include prophylactic treatment to prevent endocarditis, prosthetic joint infection and prophylactic coverage after or following sodium hypochlorite accident [39].

Indications

- Acute periapical abscesses with signs of systemic involvement.
- Acute periapical abscesses in immuno-suppressed patients.
- Prophylaxis of infection associated with tooth avulsion.
- Treatment of persistent symptomatology and/or exudation after the performance of all available options to control inter-radicular infection.
- Prophylaxis against bacteremia caused by endodontic treatment in immunosuppressed patients or patients susceptible to bacterial endocarditis.
- Abscess dissemination.
- Endodontic flare ups.

Conditions Not Requiring Adjunctive Antibiotics

- Pain without signs and symptoms of infection
- Teeth with necrotic pulps and a radiolucency
- Teeth with a sinus tract (chronic periradicular abscess)
- Localized fluctuant swellings [40]

Responsible Use of Antibiotics

- Antibiotics are used in addition to appropriate treatment to aid the host defenses in the elimination of bacteria.
- Empirical selection of an antibiotic without susceptibility tests is based on knowledge of the organisms usually involved in endodontic infections.
- Antibiotics are indicated when there is systemic involvement or evidence of spread of infection. Systemic administration of the appropriate antibiotic dosage is usually indicated for five to seven days.
- Clinical signs and symptoms will usually diminish in two to four days after diagnosis and removal of the cause of the infection.
- Patients should continue to take the antibiotic for an additional two to three days to prevent rebound of the infections.
- Noncompliance by a patient not taking the prescribed antibiotic regimen may allow a rebound of the infection. A seven-day prescription is usually adequate.
- Incision for drainage is important to remove purulent material consisting of bacteria, bacterial by-products, disintegrated inflammatory cells, enzymes and other inflammatory mediators.
- Drainage improves circulation to the infected tissues and improves delivery of a minimum inhibitory concentration of the antibiotic to the area. Because endodontic infections are polymicrobial, no single antibiotic is to be effective against all the strains of infecting bacteria.
- However, it is likely that if an antibiotic is effective against several of the strains of bacteria, it will disrupt the microbial ecosystem.
- Some patients, especially immuno-compromised patients, are at high risk for infections, and a culture of the infecting organisms with susceptibility testing may be indicated.
- Identification of the bacteria and results of susceptibility tests may take several days to a couple of weeks, depending on the microbes involved in the infection.
- Good communication with a laboratory will ensure that

the sample is properly collected, transported, cultured and identified.

- If there is any question about the patient being medically compromised, or if the patient’s condition deteriorates, referral should be considered.^[41,42]

Antibiotics used systemically (Table 3 and 4)

1. Penicillin
2. Erythromycin
3. Clindamycin
4. Clarithromycin
5. Azithromycin
6. Tetra cycline
7. Doxycycline

8. Ciprofloxacin
9. Metronidazole

Table 3: When to prescribe systemic Antibiotics in Endodontics

Symptomatic / asymptomatic apical periodontitis	No antibiotics, debridement sufficient
Acute apical abscess with systemic involvement or in immuno-suppressed patients	Local debridement and systemic Antibiotics needed
Only apical abscess	No systemic antibiotics, debridement of root canal and intracanal medicament
Cellulitis / space infection	Systemic Antibiotics needed

Table 4: Commonly used systemic antibiotics in Endodontics

Name	Mechanism	Effectiveness	Dosage And Use
Penicillin VK ^[43]	Inhibits cell wall synthesis- inhibiting transpeptidase that catalyze the final step in cell wall synthesis	facultative and anaerobic microorganisms associated with endodontic infections	A loading dose of 1,000 mg of penicillin VK should be orally administered, followed by 500 mg every four to six hours for five to seven days.
Amoxicillin- analogue of penicillin ^[44]	Inhibition of biosynthesis of cell wall mucopeptide during bacterial multiplication	Effective against gram positive than gram negative	The usual oral dosage for amoxicillin is 1,000 mg loading dose followed by 500 mg every eight hours for five to seven days.
Augmentin- The combination of amoxicillin with clavulanate ^[45]	Clavulanate is a competitive inhibitor of the betalactamase enzyme produced by bacteria to inactivate penicillin + cell wall synthesis inhibition by amoxicillin	Both gram positive and gram negative	usual oral dosage for amoxicillin with clavulanate is 1,000 mg loading dose followed by 500 mg every eight hours for five to seven days
Clindamycin- lincomycin ^[45]	Protein synthesis inhibition in bacteria by binding to 50 s ribosome	gram-positive facultative microorganisms and anaerobes also against certain gram negative organisms	oral adult dosage for serious endodontic infections is a 600 mg loading dose followed by 300 mg every six hours for five to seven days
Clarithromycin And Azithromycin- macrolide ^[45]	Protein synthesis inhibition in bacteria by binding to 50 s ribosome	Both gram positive and gram negative organisms	Oral dosage for clarithromycin is a 500 mg loading dose followed by 250 mg every 12 hours for five to seven days. The oral dosage for azithromycin is a 500 mg loading dose followed by 250 mg once a day for five to seven days
Doxycycline – tetracyclines ^[46] .	bacteriostatic, inhibiting protein synthesis by binding to 30S ribosomes	gram positive and gram negative microorganisms	100 mg (bid)
Ciprofloxacin- synthetic fluoroquinolone ^[46] .	Inhibits the enzyme bacterial DNA gyrase- bactericidal	potent activity against gram negative bacteria but very limited activity against gram positive bacteria, not effective against anaerobe	500 mg at every 12 hr
Metronidazole – nitro imidazole group ^[46] .	Redox reaction release free radicals	Effective against anaerobes	250 – 500 mg (qid)

Antibiotic prophylaxis

The protocol proposed by the American Heart Association states that antibiotics must be administered one hour (oral route) or 30 minutes (intravenous route) before the procedure (Table - 5). The principles of antibiotic prophylaxis include the following:

1. satisfactory risk and cost-benefit ratios should exist in which benefit to the patient
2. Significantly outweighs medical and financial risks.
3. The antibiotic must be in high concentrations at the target site.
4. An antibiotic loading dose (2 to 4 times the maintenance dose) must be used.
5. The antibiotic is continued only as long as microbial contamination from an operative site continues.

Conditions requiring

- Previous history of endocarditis.
- Total joint replacement.
- Complex and cyanotic congenital heart diseases.
- Surgically constructed pulmonary shunts.
- Rheumatic heart diseases.
- Mitral valve prolapse
- Valvular regurgitation
- Prosthetic valve replacement.
- Uncontrolled diabetes mellitus.^[47]

Dental procedures at high risk and low risk of Bacteremia

High risks

- Dental extractions
- Periodontal procedures – surgeries, SRP
- Dental implants placement, Reimplantation of avulsed tooth
- Endodontic instrumentation beyond apex
- Endodontic surgery, Placement of retraction cord
- Placement of orthodontic bands
- Intraligamentary and intraosseous injections

Low risks

- Restorative procedures
- Intracanal endodontic treatment and post placement and core
- Placement of rubber dam, removable partial dentures
- Orthodontic appliance adjustments
- Taking oral impressions, oral radiographs, fluoride gels application [48].

Table 5: Regimen ADA 2008 [49, 50]

			Regimen: Single Dose 30 to 60 min. Before Procedure
Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR Cefazolin or ceftriaxone	2 g IM* or IV+ 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin ϕ 5 OR Clindamycin OR Azithromycin or clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone δ OR Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV
*IM: Intramuscular +IV: Intravenous ϕ Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage. δ Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.			

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Recent advances

Nanoparticles have been found to have a broad spectrum of antimicrobial activity and less incidence of microbial resistance development than antibiotics. Nanoparticles range from 1- 100 nm in size. Nanoparticles can be organic, inorganic, metallic and functionalised nanoparticles. Nano silver, gold, zinc oxide, magnesium oxide, calcium oxide and titanium oxide have been extensively analysed and studied. The combination of nano-particles with photosensitizer molecules has emerged as a new interdisciplinary research field.

Functionalized nano-particles containing various reactive molecules and decorated with peptides or other ligands have led to new possibilities of combating antimicrobial resistance and potential drug delivers. Nano-diamonds (NDs) may offer unique advantages due to their favorable properties. Nano-diamond gutta percha composite (NDGP) embedded with nano-diamond -amoxicillin (ND-AMC) conjugates, which can

reduce the likelihood of root canal re-infection and enhance the treatment outcomes [51]. Even nanosilver coated gutta-percha was introduced in 2008 by Iranian researchers to prevent bacterial colonization in root canal space [52].

Bottino MC *et al.* suggested the use of the polymer based antibiotic containing electrospun scaffolds may act as an antimicrobial drug delivery system for regenerative endodontics. As the scaffolds degrade over time, it does not require to be removed. He also suggested the electrospun nanocomposite fibrous material acts as a scaffolds for Regenerative endodontics and also acts as a drug delivery device to aid in root maturogenesis and in the regeneration [53].

Conclusion

Since the discovery of antibiotics eight decades ago, safe use of antibiotics has revolutionized the treatment of diseases, transforming once deadly diseases into manageable health problems. However, the phenomenon of bacterial resistance, caused by the use and abuse of antibiotics and the simultaneous decline in research and development of new antimicrobial agents, is now threatening to take us back to the pre-antibiotic era. A fundamentally changed view of antibiotics is required and needs to be immediately addressed [54].

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