

SYSTEMIC USE OF ANTIBIOTICS IN ENDODONTIC INFECTIONS: A REVIEW

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Abstract: The extensive use of antibiotics and the development of antibiotic-resistant microbial strains represent a global concern, therefore during endodontic treatment these drugs should be considered mainly for patients with systemic diseases or with a localized congenital or acquired altered immunity. The prescription of antibiotics for endodontic infections is frequently empirical, which led to the increasing use of drugs with a broad spectrum, even in cases without such indications. The aim of our paper is to conduct a review on the current literature regarding the indications and use of antibiotics, in order to deliver proper recommendations for their prescription in patients under endodontic therapy. The conclusions show that amoxicillin is recommended alone or together with clavulanic acid, due to better absorption and lower risk of side effects, even though Penicillin V potassium, possibly combined with metronidazole is still effective in the majority of cases.

INTRODUCTION

Antibiotics represent an important group of drugs, whose correct use assure the resolution of infection, prevent the spreading of the disease and reduce the risk of complications. Unfortunately, almost 50% of all antibiotics are not used or prescribed correctly. Antibiotic administration can be accompanied by unpleasant symptoms such as stomach cramps, diarrhea, nausea or vomiting, due to the disturbances of the gastro-intestinal microbial flora. In prescribing oral antibiotics, of great concern is the risk of developing an infection with *Clostridium difficile*, microorganism responsible for numerous infections and a great number of deaths.(1,2) Some of the antibiotics used in endodontic infections, such as amoxicillin and clindamycin were frequently associated with *Clostridium difficile* infection, compared with metronidazole and macrolides in which the incidence of this complication is less common.(3) Antibiotics can cause other side effects, represented by the development of yeast infections as a result of an imbalance in the body's normal flora, allergic reactions, skin reactions, Stevens-Johnson syndrome, breathing difficulty or even anaphylaxis. The inflammatory process of the periradicular tissues, called apical periodontitis, is caused by microorganisms located inside the root canal. Accordingly, for the healing of these osseous lesions, the main concern is the elimination of infection from the endodontic system and prevention of re-infection. Recent epidemiological studies around the world showed that re-infection is quite a common finding, emphasizing the need for better understanding of the survival mechanisms of resistant bacteria inside root-filled canals and the interactions between therapy and endodontic flora in primary apical periodontitis. Several surveys showed that general dentists and endodontists prescribe on daily basis antibiotics for patients with dental pain (4,5), questioning whether prescribing antibiotics in these conditions is appropriate, beneficial and correct, from both medical and legal perspectives. Therefore, it would be better if dental specialists evaluated the benefits and risks of these drugs and made an informed decision with their patients regarding the use of antibiotics in these situations.

Dentists prescribe approximately 10% of antibiotics dispensed in primary care, therefore their contribution to the development of antibiotic resistant bacteria should not be underestimated.(6) Data from United Kingdom reported that antibiotics are prescribed three times weekly by 40% of dentists while 15% prescribed these drugs daily.(7) In dentistry, the prescription of antibiotics is empirical, due to the dentist's lack of knowledge regarding the correlation between specific microorganisms and the oral infection sustained by these strains, as microbiological samples from the root canal or apical region are not usually indicated and analyzed. Therefore, the microorganisms responsible for endodontic infections are usually only being suspected and the treatment based on using broad-spectrum antibiotics.(8) The inappropriate use of antibiotics promotes the development of antibiotic resistance, misuses the therapy resources and increases the risk of anaphylactic reactions.(6,9) The indiscriminate use of antibiotics facilitated the selection of microorganisms resistant against beta-lactam antibiotics, through mechanisms as expression of penicillin-binding proteins with lower affinity to these drugs or production of penicillinase (a beta-lactamase enzyme). In addition, prescribing antibiotics for common medical problems increases the patient's expectations for these drugs and leads to a vicious cycle in which the dentist increases prescribing in order to meet expectations; furthermore, it exposes people to unnecessary side effects.(6) Several studies have shown that antibiotics do not reduce pain or swelling induced by symptomatic apical pathology (6,10-12) and furthermore, a Cochrane systematic review found no evidence in supporting the use of antibiotics in pain relief during irreversible pulpitis.(13,14) Two systematic reviews (15,16) showed that in order to justify antibiotic therapy, the infection should be systemic or the patient febrile or with compromised immunity.(17) Therefore, prescription of antibiotics by dental professionals should be limited.(18) Endodontic infections are known to be a combination of Gram-positive, Gram-negative, facultative anaerobes and strict anaerobic bacteria (19) and after becoming resistant to antibiotics, these microorganisms have the ability to exchange

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CLINICAL ASPECTS

this resistance.(20) In the oral cavity, studies have shown a gradual reduction in antibiotic sensitivity of the biofilm, a phenomenon reported for drugs such as penicillin, macrolides and clindamycin and an increasing number of resistant species, such as *Porphyromonas*, *Prevotella*, alpha- haemolytic streptococci or *Streptococcus viridans*.(21,22)

Systemic use of antibiotics for endodontic infections

Systemic antibiotics should be rarely used during endodontic treatment, as they should not represent a routine step in the treatment of apical periodontitis. However, one argument to prescribe these drugs was to minimize the occurrence of post-operative pain, but it was proved that this could not reduce the incidence of acute problems or flare-ups after the initiation of endodontic therapy. Furthermore, there is no scientific support for the idea that systemic antibiotic therapy could have a beneficial effect on the long-term success of the endodontic treatment of teeth with chronic apical periodontitis. Therefore, at present there is a consensus among specialists that systemic antibiotics should be prescribed only when there are general indications for their use. These include situations when infections appear to be spreading, the patients develop fever, indicating the failure of local host responses or when the host defense mechanisms are known to be compromised, the patient being at an increased systemic risk. Due to the fact that the effect of systemic antibiotic is never fully predictable, as a result of numerous factors that might affect the treatment outcome, the focus of endodontic treatment should be on using local antibacterial procedures, such as mechanical and chemical preparation of the root canals.

Indications for systemic antibiotics

According to Segura-Egea et al (23), the use of adjunctive systemic antibiotic treatment associated with endodontic therapy is indicated in:

- Acute apical abscess in medically compromised patients (systemic disease which alters the host immunologic response);
- Acute apical abscess with systemic involvement (temperature $>38^{\circ}\text{C}$, localized fluctuant swellings, malaise, trismus, local lymphadenopathy);
- Progressive infections (rapid onset of severe infection in less than 24 h, cellulitis, osteomyelitis) where the referral to oral surgeons is necessary;
- Persistent infections (presence of chronic exudation which was not resolved by intracanal medication);
- Replantation of avulsed permanent teeth (23), when topical administration of antibiotics should also be indicated.(21)
- Trauma of the soft tissue requiring treatment (debridement, sutures).

The guidelines of American Association of Endodontics (AAE) presented in 2017 (24) consider that antibiotics should be used only as adjuvant therapies when there is evidence of systemic involvement, characterized by fever, cellulitis, malaise and/or lymphadenopathies, following correct endodontic mechanical and chemical instrumentation and abscess drainage, if necessary (table no. 1). In addition, patients with compromised immunity or predisposing conditions (endocarditis) should receive antibiotic treatment as a prophylactic measure; administration of antibiotics in other circumstances has no evidence of benefit.(15,16) According to results from clinical studies, prescription of antibiotics proved to have no effect in the treatment of irreversible pulpitis, acute apical periodontitis or apical abscess, when adequate root canal treatment associated if necessary with incision for drainage was achieved. In cases with signs of spreading infections, the use of broad-spectrum antibiotics should be reduced as much as possible; the specialist should choose the shortest effective

course of antibiotic and closely monitor the patient's evolution.

Table no. 1. Management of difficult cases of endodontic treatment followed by incision

| Signs/Symptoms | Suspected condition | Therapeutic measures |
|-------------------------------------|---|---|
| Persistence of pain and/or swelling | Microbial resistance to antibiotic Inaccessible root canal areas | Use of a supplement antibiotic, such as Metronidazole |
| Trismus, dysphagia and dyspnea | An infection that is spreading to facial spaces | Hospitalization |
| Headache, visual problems | The involvement of cavernous sinus | Hospitalization |
| Fever, malaise, lethargy | Massive systemic involvement Potential septic shock | Hospitalization |

(Adapted from Segura-Egea et al. 2017)

Contraindications for systemic antibiotics

The use of antibiotics is based on obtaining the minimal inhibitory concentration effective against microorganisms at the infection site. In long-lasting endodontic infections, the dental pulp has lost the blood supply therefore by oral administration no drug can reach inside the root canal, where the infection is located. Moreover, if an apical abscess is present, it will further compress the blood vessels in the periapical area and through the cellular debris and proteins contained in the pus will be able to bind and block the antibiotics, reducing their efficiency in the absence of proper drainage. Most of the endodontic infections are restricted to the root canals and therefore can be treated successfully based on the cleaning and shaping principles of modern endodontology.(25) Therefore, based on present available data, the use of systemic antibiotics is contraindicated in the following cases:

- Symptomatic irreversible pulpitis (pain, with no other signs or symptoms of infection);
- Pulp necrosis (teeth not responding to vitality tests);
- Symptomatic apical periodontitis (pain to biting and percussion, widening of the periodontal ligament space);
- Chronic apical abscess (presence of a sinus tract, periapical radiolucency);
- Acute apical abscess without systemic involvement (localized fluctuant swellings).(13,23)

According to current knowledge and based on the guidelines of the International Association of Dental Traumatology (IADT) (26), systemic antibiotic administration is not indicated during the treatment of tooth fractures, concussions, subluxations and luxation extrusions.

Types of antibiotics and recommended dosages

The first line of antibiotics mostly used in both Europe and United States as adjunct therapy for endodontic infections are penicillin V potassium and amoxicillin.(18,23,27,28) These are beta-lactam antibiotics that bind and have an inhibitory effect on the activity of bacterial proteins involved in the synthesis of the peptidoglycan cell wall in susceptible Gram-positive and Gram-negative microorganisms.(29) These drugs proved to be highly effective against bacterial species isolated from endodontic infections that are represented mainly by facultative and obligate anaerobes.(20) In many surveys, the antibiotic mostly prescribed as an adjunct to specific therapeutic measures for endodontic infections with systemic effects is amoxicillin alone or in combination with clavulanic acid.(4,18,30,31) It is considered a moderate-spectrum antibiotic, representing a synthetic improvement of the original penicillin molecule. It is absorbed better than penicillin, can be

CLINICAL ASPECTS

used in lower doses and has less gastrointestinal effects, therefore was frequently used for oral infections. The spectrum against Gram-negative bacteria is broader compared to penicillin and the blood levels are maintained for a longer time. Amoxicillin is susceptible to degradation by beta-lactamase producing microorganisms and usually is associated with clavulanic acid, combination which is one of the most recommended in the treatment of endodontic infections.(23,32) (table no. 2).

Table no. 2. Studies on antibiotics most frequently prescribed in Europe

| Authors | First used antibiotic | Second used antibiotic | Antibiotics used in allergic patients |
|-------------------------------|-----------------------|---------------------------|---------------------------------------|
| Dailey & Martin (2001) | Amoxicillin | Amoxicillin/Metronidazole | – |
| Rodriguez-Nunez et al. (2009) | Amoxicillin | Metronidazole/Spiramycin | Clindamycin |
| Mainjot et al. (2009) | Amoxicillin | Clindamycin | Erythromycin |
| Segura-Egea et al. (2010) | Amoxicillin | Clindamycin | Clindamycin |
| Kaptan et al. (2013) | Amoxicillin | Clindamycin | Clindamycin |
| Peric et al. (2015) | Amoxicillin | Clindamycin | Clindamycin |

(Adapted from Segura-Egea et al. 2017)

It has a wide spectrum, high antibacterial effect and low incidence of resistance demonstrated in bacteria cultivated from infected root canals.(33) For patients with hypersensitivity to penicillin, clindamycin is the first drug of choice, proved to be effective against 75% of endodontic pathogens. It is a lincosamide antibiotic that binds to a ribosomal subunit inside the bacterial cell and suppresses its protein synthesis. The effect is mainly bacteriostatic, but bactericidal action can be reached using therapeutic doses. It has a very good spectrum and is active against facultative and obligate anaerobic bacteria. Using oral administration, clindamycin is not impaired by food consumption, being quickly absorbed and widely distributed in all tissues including bone and reaching peak plasma levels within 1 hour (9µg/ml after a loading dose of 600 mg in adults). This antibiotic can cause severe gastrointestinal reactions, therefore patients with penicillin allergy or history of pseudomembranous colitis, need other antibiotics such as tetracyclines, macrolides or quinolones. Unfortunately, endodontic pathogens are less sensitive to these drugs and an increased number of resistant strains have been reported. Antibiotics must be used at the correct dose, frequency and treatment duration, so that the minimal inhibitory concentration is surpassed and development of negative side effects or selection of resistant microorganisms is prevented. (34) According to a recent review made by Segura-Egea et al. in 2017, for penicillin V potassium a loading dose of 1000 mg administered orally, followed by 500 mg every 4–6 hours is recommended; for amoxicillin 1000 mg loading dose with or without clavulanic acid, followed by 500 mg every 8 hours. (23) If the therapy with penicillin V potassium is ineffective, its combination with metronidazole using a loading dose of 1000 mg followed by 500 mg every 6 hours or amoxicillin with clavulanic acid should be prescribed. If this approach will have no positive response, the need of an interdisciplinary consultation with a clinical microbiologist or an infectious disease specialist should be evaluated. There are numerous cases in which beta-lactam antibiotics cause allergies and if a true penicillin allergy was confirmed, alternative antibiotics might be clindamycin (600 mg loading dose followed by 300 mg every 6

hours), clarithromycin (500 mg loading dose followed by 250 mg every 12 hours) or azithromycin (loading dose of 500 mg followed by 250 mg once a day).(23,35) The best indication for treatment duration is represented by the clinical improvement of symptoms; when these have resolved and there is evidence of healing, the antibiotic treatment should be discontinued.(36) The patients must be evaluated after 2-3 days in order to determine the clinical condition and the effectiveness of the treatment; usually, an interval of 3–7 days is enough to control the infection and some authors consider that after 3 days further treatment should be indicated only if it seems to be clinically necessary.

CONCLUSIONS

Antibiotics are essential therapeutic agents and special attention should be directed to their overuse and misuse, as these could lead to the development of resistant bacteria. In order to avoid the extensive prescription of antibiotics and to improve the specific methods of treatment, modern endodontic therapy is characterized by considerable research effort in order to develop new methods and materials for root canal instrumentation, irrigation, disinfection and filling, aiming to a greater possibility of complete elimination of endodontic infection and healing.

Up to date, there is no scientific data to support the idea that the use of systemic antibiotics might have a beneficial effect on the long-term success of the treatment of apical periodontitis. With today's materials and techniques, excellent treatment outcomes can be achieved, but future developments in these areas will hopefully further improve the management of the root canal infection. Most specialists agreed that the high quality in the various steps of conventional endodontic treatment represents the key factor for increasing the long-term treatment success, better prevention and healing of apical periodontitis.

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