american association of endodontists

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AAE Guidance on the Use of Systemic Antibiotics in Endodontics

AAE Position Statement

INTRODUCTION

The spectrum of endodontic pathosis includes many conditions for which dentists and endodontists determine that it is appropriate to prescribe antibiotics. Some of these conditions involve purely an inflammatory reaction, and some involve various stages of infection. This infection may be localized to the pulp and periapical tissues, and it may be spreading to regional lymph nodes, or systemically. This document is intended to present the available evidence related to prescribing antibiotics, highlight appropriate clinical recommendations and identify gaps in knowledge for which personal judgment is the best guide for assessing risks and benefits in this practice.

This document is not intended to be an exhaustive systematic review on the subject. It will also not address the systemic or topical application of antibiotics following traumatic injuries to teeth (which are addressed in other AAE guidelines), and the use of antibiotics as intracanal medicaments. Finally, this document is not intended to present new knowledge in the field.

Overall risks and benefits of prescribing systemic antibiotics

Antibiotics are an important class of drugs. Clearly, the benefits of correct use of antibiotics include the resolution of infection, prevention of the spread of disease and minimization of serious complications of disease. Up to 50% of all antibiotics are prescribed or used incorrectly. Risks associated with the use of antibiotics include nausea, vomiting, diarrhea and stomach cramps because of the disturbances of the gut microflora.

A particular concern to the use of oral antibiotics is the development of *Clostridium difficile* infection. *C. difficile* was responsible for almost half a million infections and was associated with approximately 29,000 deaths in 2011 (1). Among the antibiotics prescribed for endodontic infections, clindamycin, amoxicillin, cephalosporins are commonly associated with *C. difficile* infection, whereas macrolides and metronidazole are less commonly so (2). Other side effects include the development of yeast infections in the mouth or vagina, again resulting from an imbalance in the body's normal flora. Antibiotics can also cause allergic reactions ranging from rash, skin reactions, Stevens-Johnson syndrome to breathing difficulty and anaphylaxis.

About This Document
This paper is designed to provide scientifically based guidance to clinicians regarding the use of antibiotics in endodontic treatment.
Thank you to the Special Committee on Antibiotic Use in Endodontics: Ashraf F. Fouad, Chair, B. Ellen Byrne, Anibal R. Diogenes, Christine M. Sedgley and Bruce Y. Cha.

The guidance in this statement is not intended to substitute for a clinician's independent judgment in light of the conditions and needs of a specific patient.

Antibiotics are essential medications but their overuse and misuse are creating resistant bacteria that are not susceptible to any antibiotics. Each year at least two million people in the U.S. become infected with multidrug resistant bacteria and 23,000 deaths have been attributed to these infections (3, 4).

Use of adjunctive antibiotics in addition to adequate debridement and surgical drainage

The key to successful management of infection of endodontic origin is adequate debridement of the infected root canal and drainage for both soft and hard tissue. The objectives for treatment of infections of endodontic origin are removal of the pathogenic microorganisms, their by-products, and pulpal debris from the infected root canal system that caused the periapical pathosis and establishment of conditions favorable for the lesion to resolve. In addition to adequate debridement of the root canal system, localized soft tissue swelling of endodontic origin should be incised and drained concurrently. Studies have shown that adjunctive antibiotics are not effective in preventing or ameliorating signs and symptoms in cases with irreversible pulpitis, symptomatic apical periodontitis, or localized acute apical abscess, when adequate local debridement, medication and incision for drainage, if indicated, have been achieved (5-11).

When using adjunctive antibiotics in addition to adequate debridement and surgical drainage, such as in cases with spreading infections, the practitioner should use the shortest effective course of antibiotics, minimize the use of broad-spectrum antibiotics and monitor the patient closely.

Use of antibiotics in the absence of adequate debridement and surgical drainage

As noted before, there is evidence from randomized clinical trials and systematic reviews to indicate that supplemental antibiotics following adequate debridement and drainage in cases of localized endodontic infections is ineffective (5-8). It is also the standard of care to prescribe primary or adjunctive antibiotics in conjunction with local debridement and surgical drainage for patients who have spreading infections, and to monitor their progress closely as these prescriptions are made empirically and may be ineffective or insufficient for adequate treatment.

However, the literature is not clear on indications, efficacy or duration of antibiotics for cases in which the practitioner is not able to render local debridement and drainage at the time of patient presentation, or in cases that are complex and the efficacy of local treatment may not be completed. In these cases, it is not known whether systemic antibiotic therapy would provide sufficient relief of symptoms and prevention of spread of infection to warrant a prescription, since etiology of the infection may not have been fully addressed. Furthermore, the answer to these questions may not be feasible to determine through objective research in the future, as the necessary study design may be considered unethical to patients.

The literature contains many studies that may not reach contemporary design standards that eliminate bias in research, and much anecdotal evidence that promote prescription of antibiotics for the patient's comfort and to alleviate their apprehension (12-14). Likewise, there are several surveys that show that both general dentists and endodontists routinely prescribe antibiotics for patients with dental pain (15, 16). This leads to the question of whether prescribing antibiotics for patients in these situations is appropriate, warranted and defensible from a medico-legal perspective.

This controversy is somewhat similar to that surrounding the need for, and efficacy of, prophylactic antibiotics in cases where there is little evidence to their efficacy. An example of this would be to prevent late prosthetic joint infection following a dental appointment. However, what is different here is the concern about patient comfort and fear of spreading of the infection systemically. The issue is further complicated by the fact that many patients perceive improvement in their condition after taking antibiotics, at least in part due to a strong placebo effect that antibiotics may have (17).

Ultimately, dentists and endodontists must weigh the benefits and risks of antibiotics, as previously stated, and make an informed decision with their patients on the appropriateness of using antibiotics in these cases. One strategy that may be useful is to educate the patient about the signs and symptoms of a spreading infection and give the patient a "stand-by" antibiotics prescription. The patient would only fill the prescription and call the prescriber's office, if he/she perceives this type of infection to be occurring, prior to receiving definitive care.

Comparison of the efficacy of different types, dosage and duration of antibiotics

The therapeutic use of antibiotics relies on achieving at least the minimal inhibitory concentration (MIC) of the drug, against sensitive microorganisms in the site of infection. In the case of advanced endodontic infections, the dental pulp tissue after succumbing to liquefaction necrosis is no longer vascularized, and orally administered drugs are unable to reach the site of infection. Therefore, the drug distribution is restricted to the surrounding vascularized tissues. However, in cases of apical abscess, the presence of pus limits vascular supply, and contain cellular debris and proteins that can bind and sequester antibiotics making these drugs less effective in the absence of adequate drainage (18).

Thus, antibiotics should only be used as adjuvant therapies in cases with evidence of systemic involvement (fever, malaise, cellulitis and/or lymphadenopathies) following adequate endodontic disinfection and abscess drainage if swelling is present (8, 19). In addition, patients who are immunocompromised or have predisposing conditions such as previous endocarditis should be medicated as a prophylactic measure. It is important to note that administration of antibiotics in the absence of the above-mentioned reasons has no evidence of therapeutic benefit (6, 9). Lastly, in the cases of a therapeutic indication, the choice of the antibiotic agent, dosage and duration is typically made in an empirical fashion.

Penicillin VK and amoxicillin, both beta-lactam antibiotics, are the first line of antibiotics chosen as adjunct therapeutic agents in endodontics in the United States of America and Europe (20-22). These drugs act by binding and inhibiting the activity of several bacterial proteins called penicillin binding proteins (PBP) involved in the synthesis of the peptidoglycan cell wall in susceptible both gram-positive and gram-negative bacteria (23). These drugs have been found to be highly effective against isolates from infected root canal systems that are composed primarily of facultative and obligate anaerobes (24-26, 35).

Amoxicillin demonstrates greater efficacy and therapeutic value because:

1. It has broader spectrum and is more effective than penicillin VK against certain gram-negative anaerobes due to better microbial penetration;
2. It is more readily absorbed from the gastrointestinal (GI) tract than penicillin VK, which is poorly absorbed and its accumulation in the GI tract is associated with depletion of commensal flora and digestive disturbances;
3. Its absorption is not impaired by food reaching peak plasma levels within 2 hours of ingestion;
4. Only approximately 20% of absorbed amoxicillin is protein-bound in the plasma, being more readily available;
5. It has significantly greater half-life than penicillin VK requiring doses to be taken 2-3 times a day as opposed to 4 times daily for penicillin VK (23, 27, 28).

The recommended dose regimen for amoxicillin is 500 mg three times a day (with or without a loading dose of 1,000 mg) for adults. Although these doses are well established based on pharmacokinetic studies and designed to establish maximum effective doses in the plasma, there is far less evidence to support the duration of treatment. Most practitioners usually prescribe antibiotics in courses of 3 to 7 days (15, 29). Interestingly, some evidence suggests that perhaps shorter courses (2-3 days) may be successfully used as adjuvant therapies (30, 31). The decision of using antibiotics for longer periods (7 to 10 days) is largely based on studies and clinical practice of treating infections whose etiology is not fully identified or the treatment of bloodstream infections in hospitalized patients.

This clinical indication and use of antibiotics differ from the endodontic use as an adjunct therapy to limit the spread and the systemic manifestation of the infection following adequate surgical debridement and establishment of drainage. Moreover, therapies lasting 7 days with amoxicillin have been shown to increase the population of resistant strains (32). It is estimated that approximately 30% of severe dento-alveolar infections have strains resistant to penicillin-like drugs (33). Increased presence of resistance strains has been associated with over-prescription of this class of drugs.

This indiscriminate antibiotic use has selected strains that possess many resistance mechanisms against beta-lactam antibiotics. These include:

1. constitutive expression of high molecular weight penicillin-binding proteins (PBP) that have lower affinity to beta-lactam antibiotics;
2. expression of beta-lactamase (also known as penicillinase) enzymes and
3. drug efflux pumps, particularly in certain gram-positive strains (34).

For this reason, if symptoms are not improved after endodontic debridement and/or drainage, amoxicillin may be combined with clavulanic acid (125 mg bid or tid), which is a beta-lactamase inhibitor and increases the susceptibility of penicillin resistant strains.

This combination has been shown to be effective against 100% of cultivable endodontic bacteria, increasing the spectrum of amoxicillin in persistent infections (25, 35, 36). However, the use of amoxicillin/clavulanic acid combinations should not be done indiscriminately as there are potentially significant side effects that include gastrointestinal and hepatic disturbances (37).

Although penicillin and amoxicillin are the most prescribed antibiotics, they have a side effect profile that ranges from gastrointestinal disturbances, hepatic toxicity to severe anaphylactic allergic reactions. It is estimated that approximately 8% of the population using health care in the U.S. have allergic reactions to penicillin (38). There is well-reported cross-reactivity of penicillin allergy with cephalosporins (39), with a total prevalence of 1% of the American population taking antibiotics being also allergic to cephalosporins (38).

In susceptible patients, immunoglobulin E (IgE) against breakdown products of penicillin is readily detected in patients with a history of penicillin allergic reactions (40). Anaphylactic types of reactions are the most severe manifestation of allergy to beta-lactam antibiotics but are the least prevalent (41). Thus, these drugs should be avoided in patients with a previous history of hypersensitivity, or discontinued in patients without a history but with presentation of hypersensitivity, to avoid life-threatening anaphylactic reactions.

Clindamycin is the first drug of choice for patients with a history of hypersensitivity to penicillin drugs. This drug is a lincosamide antibiotic that acts by binding to the 50S ribosomal subunit, suppressing protein synthesis (42). Therefore, its effects are mainly bacteriostatic, although bactericidal effects can be achieved with therapeutic doses. It has been shown to be effective against 75% of cultivable endodontic pathogens (35, 36, 43). It has very good spectrum, with coverage against both facultative and obligate anaerobic bacteria.

Clindamycin is readily absorbed after oral administration, which is not impaired by concomitant food consumption, reaching peak plasma levels in 1 hour (9 µg/ml after a loading dose of 600 mg in adults). The drug is widely distributed in the body, including bone (44). The recommended dosage for infections of endodontic origin is 600 mg as a loading dose followed by 300 mg every 6 hours, whereas in children, this dose must be adjusted to 10-30mg/Kg (dose/ body weight) divided into 4 equal doses.

Similar to other antibiotics used as adjuvants in endodontic therapy, there is no agreement on the duration of the treatment and the perceived therapeutic benefit. Also, prolonged use of this antibiotic will increase the likelihood of untoward effects and selection of resistant bacterial strains.

Despite its excellent pharmacokinetics and moderate effectiveness against endodontic pathogens, its use can be associated with significant side effects. Gastrointestinal disturbances are the most common side effect with an approximately eight-fold increased risk of developing C. difficile infection than the use of penicillin (45) that can evolve into pseudomembranous colitis, a potentially fatal disease. Thus, administration of this drug must be discontinued upon the first signs of this disease (i.e. diarrhea with fever, abdominal pain, mucus and blood in the stool) and the patient referred to a primary care physician for treatment that may involve prescription of metronidazole orally or intravenously.

Caution should be employed when prescribing this medication for patients with history of clindamycin-associated pseudomembranous colitis (46). Thus, patients with a history of penicillin allergy and severe gastrointestinal reactions to clindamycin require alternative antibiotics such as macrolides, quinolones or tetracyclines. Unfortunately, endodontic pathogens have lesser susceptibility to these alternative antibiotics with increased prevalence of resistant strains (28, 35, 43).

Indications for performing culture and sensitivity tests

As noted, antibiotics are prescribed empirically by practitioners. Occasionally, despite adequate local debridement and antibiotic coverage, the treatment is ineffective and the patient's condition deteriorates. The patient may have unusual species of virulent bacteria, multidrug resistant bacteria and/or fungal infection. He/she may also have immune deficiency, uncontrolled diabetes, penicillin allergy and/or a history of *C. difficile* infection. In these situations, culture and sensitivity testing may assist the practitioner in selecting the appropriate antibiotic. It is generally recognized, however, that most oral bacterial species are commensal organisms, that about half of them are not cultivable, and that the effectiveness of antibiotics is variable in polymicrobial infections. Therefore, this testing may only provide additional guidance to the practitioner, in conjunction with surgical debridement.

Signs and Symptoms	Possible Condition	Management Strategies
Continued pain and/or swelling	Bacterial resistance to antibiotic or presence in inaccessible areas	Supplementing antibiotic regimen with another oral drug such as Metronidazole
Trismus, dyspnea and dysphagia	Spread to poorly vascularized fascial spaces such as submandibular, sublingual, masseteric, parapharyngeal and retropharyngeal spaces	Hospitalization, culture and sensitivity, together with IV antibiotics
Vision problems, headache	Cavernous sinus involvement	Hospitalization, culture and sensitivity, together with IV antibiotics
Fever over 102°F, malaise, lethargy and increased erythrocyte sedimentation rate	Massive systemic involvement, potential septic shock	Hospitalization, culture and sensitivity, together with IV antibiotics

Table: Unfavorable response to empirically prescribed antibiotics following root canal debridement, and incision for drainage.

Aspiration of a purulent fluid is the optimal sampling method, and is achieved using a 16 or 18-gauge needle. This is taken promptly to the microbiological laboratory to promote growth of strict anaerobes (47). The use of swabs to sample more superficial infections is less effective, due to the possibility of contamination or death of anaerobes. Optimally, these swabs should be promptly stored in pre-reduced transport media, such as Liquid Dental Transport Medium (Anaerobe Systems, Morgan Hill, CA). Culture and sensitivity testing is a slow process, which typically takes three to six days. Due to the urgency of the situation, deeper drainage and debridement may be indicated, and the patient is started on other antibiotics or multiple drugs, until the test results are obtained.

Studies show that beta-lactam antibiotics are the optimal drugs for endodontic pathogens, and that there is very little bacterial resistance to amoxicillin with clavulanic acid (25, 35, 36, 48). These studies have demonstrated more resistance to clindamycin, which has typically been the drug of choice for penicillin-allergic patients. Therefore, in penicillin-allergic patients, other drugs such as moxifloxacin or azithromycin should be considered (49, 50).

Prophylactic use of antibiotics for endodontic surgery

Prophylactic use of antibiotics to prevent postoperative infections is common in general and oral surgery. Factors involved in the decision of whether to prescribe prophylactic antibiotics, and whether to provide one preoperative dose or a prolonged course, include the type and site of surgery, the morbidity associated with potential infection, and the systemic health of the patient. One randomized clinical trial compared giving 256 patients undergoing endodontic surgery either preoperative 600 mg tablet of clindamycin or placebo (51). The results were that four patients in the placebo group and two in the clindamycin group developed postoperative infection, and this difference was not statistically significant. However, the average surgical time in this study was only about 30 minutes in both groups, and the overall number of infections was low. There are no data available for endodontic surgery that may take a longer period or are performed in practices that have higher rates of postoperative infections.

Nevertheless, there is evidence that antibiotic prophylaxis may reduce postoperative infection following exodontia and surgical osteotomy extraction (52, 53). In addition, there is one study that showed that peri-operative antibiotic prophylaxis significantly reduced the incidence of bisphosphonate-related osteonecrosis of the jaw, in multiple myeloma patients on IV bisphosphonates undergoing dental surgery (54).

In cases where the biopsy result indicates periapical actinomycosis infection, it does not appear that antibiotic treatment is indicated, as the surgical procedure is associated with curettage of the infected tissues in these cases (55).

Association between adjunctive antibiotics and periapical healing

The effect of perioperative antibiotics on long term healing of nonsurgical and surgical endodontics has not been sufficiently studied. One study compared the healing of apical periodontitis in 62 patients who underwent nonsurgical root canal treatment (56). There was no difference between the penicillin and the control groups in healing. A more recent endodontic prospective cohort study showed no association between the use of long-term antibiotics and nonsurgical treatment or retreatment outcome (57).

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