Endodontics and Antibiotic Update

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Estimates suggest that pulpal disease may affect up to 30% of the world's population. When left unchecked, pulpal disease lends itself to a reduced quality of life by means of increased pain, loss of physiologic function and compromised anatomical form of the affected dentition. Scientific literature consistently highlights the undeniable benefits of antibiotic use in treatment of disease control, more specifically odontogenic bacterial infections. However, the value of these drugs in preventing serious health complications is not always congruent with safety; because their use can be undermined by disruptive prescribing practices and behaviors that lead to misuse of antibiotics and their associated adverse effects (1).

Guidelines for proper prescription of antibiotics in helping to manage polymicrobial infections have remained consistent throughout the endodontic literature, although recent updates warrant mention, according to a new report by the American Dental Association (17). Classic literature consistently illustrates that a regimen of systemic oral antibiotics is not indicated for a small localized swelling in the absence of systemic signs and symptoms of infection or spread of infection (2). A recent Cochrane Database Systematic review showed that antibiotics were of no additional therapeutic benefit for healing of a localized periapical abscess. Outcomes of pain and infection were dependent upon drainage being relieved through access or incision and drainage (3). Evidence shows that antibiotics are an adjunct in the management of periradicular infections. In an effort to save the natural dentition, effective treatment of odontogenic infections must include removal of the reservoir of infection through endodontic treatment.

Endeavors to better identify factors influencing safe and recommended antibiotic prescribing regimens have galvanized worldwide attention, with the World Health Organization leading the way to safeguard against antibiotic resistance (4). The role of dentistry in the phenomenon of antibacterial resistance from over prescribing has yet to be quantified but cannot be denied. According to the Centers for Disease Control, in 2011 dental professionals wrote

Chart 1. Oral antibiotic prescribing by provider type — United States, 2011

PROVIDER SPECIALTY	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER PROVIDER, RATE
Primary Care Physicians	134.9	568
Physician Assistants and Nurse Practitioners	38.5	222
Surgical Specialties	23.0	187
Dentistry	20.8	233
Emergency Medicine	14.7	454
Dermatology	8.5	746
Obstetrics/Gynecology	7.2	191
Other	25.7	124
All Providers	273.3	300

Chart 2. Oral antibiotic prescribing by provider type — United States, 2016
For each provider specialty, number of prescriptions and rate per provider

PROVIDER SPECIALTY	NUMBER OF ANTIBIOTIC PRESCRIPTIONS (MILLIONS)	ANTIBIOTIC PRESCRIPTIONS PER PROVIDER, RATE
Primary Care Physicians	106.3	448
Physician Assistants and Nurse Practitioners	68.4	395
Surgical Specialties	19.3	217
Dentistry	25.7	210
Emergency Medicine	14.7	454
Dermatology	6.9	608
Obstetrics/Gynecology	6.0	160
Other	22.9	110
All Providers	270.2	296

nearly 21 million prescriptions.

(Chart 1, reference 5) Almost 50% of those antibiotics were either prescribed or used incorrectly. These statistics create a stark reality of the concern needed for proper prescription guidelines to be upheld (6). Data from the same CDC database highlights an alarming upward trend. In 2016, nearly 26 million oral systemic antibiotic prescriptions were written by dentists alone. That's nearly 10% of all prescriptions written in the outpatient setting by the provider types as classified by the American Medical Association (Chart 2, reference 5). This pattern is mirrored in British Columbia, Canada, where, from 1996 to 2013 antibiotic prescriptions by physicians decreased, whereas that of dentists increased by more than 62.2% (7). More conservative estimates of prescribing habits of a specific cohort of U.S. dentists showed the rate of antibiotic prescribing practices by general dentists remained stable during the three-year study period (2013-2015), and despite a slight decrease in antibiotics used for indeterminate and prophylaxis purposes, approximately 14% of antibiotic prescriptions were deemed inappropriate, based on the antibiotic prescribed, antibiotic treatment duration or both indicators (8).

These statistics are concerning. In dentistry, antibiotic prescriptions should mainly be therapeutic based on clinical signs, symptoms or clinical conditions. Antibiotic prescriptions may also be prophylactic with a primary focus on prevention of infective endocarditis and or prosthetic joint implant infection. Dentists should rarely prescribe oral systemic antibiotics for primary therapy or as a first-line treatment for an infection (9).

Influencing prescription patterns has challenges because not all clinicians have access to or actively search for the most up to date evidence based recommendations. However, many dentists acquire knowledge through peer-reviewed sources and educational platforms (10). Evidence further shows that information gained through these various outlets can impact patterns and influence antibiotic stewardship leading to better prescribing habits.

This issue of *Colleagues* provides recommended best practices and updates within the literature on antibiotic prescribing for clinical and nonclinical indications. Reviewing the following guidelines may help to establish general practices to aid us in making clinical decisions regarding the use of antibiotic therapy, lending to safer and more effective habits.

Endodontic Infection

Endodontic disease can be primary or secondary infections characterized by a polymicrobial nature which lends to biofilm formation. Microbial biofilms in the root canal are highly complex, multi-species entities that amplify the difficulty in eradication of the microbial biomasses. The bacterial microflora of the root canal is initially dominated by aerobes and facultative anaerobes (11). As disease progresses, the ecology within the root canal system changes and is largely characterized by anaerobic bacteria in primary infections. The most common species of bacteria isolated in odontogenic infections are the anaerobic gram-positive cocci *Streptococcus milleri* group and *Peptostreptococcus*. Anaerobic gram-negative rods, such as Bacteroides *(Prevotella)* also play an important role. In general, primary infection involves pulp inflammation and root canal infection following invasion by microbes or microbial by-products, eventually resulting in inflammation of the supporting tissues causing apical periodontitis. Secondary infection (or post-treatment infection) occurs either as reinfection (acquired or emergent), remnant (persistent) infection or recurrent infection (re-developed in teeth after apparent healing) in teeth that have been previously root canal treated (12). The microbial flora found in secondary infections, typically are able to survive harsh conditions such as a wide pH range and nutrient-limited conditions. There is a definite contrast in the microbial phenotypes in primary infections as compared to secondary infections, more specifically the latter being predominated by gram-positive bacteria.

Whether primary or secondary involvement, infection will spread and the inflammatory response will progress until the source of the irritation is managed or eliminated. A thorough evaluation [including past history, clinical evaluation and relevant imaging modalities] is paramount for proper diagnosis and appropriate treatment of the source of infection. It is imperative that the source of infection be addressed expeditiously. Placing a patient on antibiotics and rescheduling to have the source dealt with at a later time is not sound practice and may allow the infection to worsen. Generally, an accurate diagnosis coupled with effective endodontic treatment will decrease microbial flora sufficiently for healing to proceed (13).

Treatment of Endodontic Infection

Objectives of endodontic treatment include removal of the etiologic agent (microbes and byproducts), debris and inflammatory mediators from the infected root canal system (14). In essence this allows the host to regain a favorable condition promoting health and letting the periapical tissues return to a state of reduced inflammation/infection. Evidence based reviews highlight very specific indications for prescribing antibiotics preoperatively or postoperatively

Table 1. Indications for Adjunctive Antibiotics

Acute Apical Abscess in Immunocompromised Patients
• Localized fluctuant swellings
• Patient with systemic disease causing impaired immunologic function
Acute Apical Abscess in Immunocompetent Patients *(When same visit treatment is not an option)*
• Localized fluctuant swellings
Acute Apical Abscess with Systemic Involvement
• Elevated body temperature >100˚F
• Malaise
• Unexplained trismus
• Lymphadenopathy
Progressive Infections
• Rapid onset of swelling <24hrs
• Cellulitis or a spreading infection
• Osteomyelitis
Persistent Infection
• Chronic exudation, which is not resolved by regular intracanal procedures and medications

Table 2. Conditions NOT Requiring Adjunctive Antibiotics

Pain Without Signs and Symptoms of Infection
• Symptomatic irreversible pulpitis
• Symptomatic apical periodontitis (Pain to percussion and biting)
Teeth with Necrotic Pulps and a Radiolucency
Teeth with a Sinus Tract/Parulis (Chronic Apical Abscess)
Acute Apical Abscess in Immunocompetent Patients *(When same visit treatment is an option)*
• Localized fluctuant swellings

to prevent endodontic infection or pain; moreover when the infection becomes systemic (Table 1).

In other words, antibiotics are not indicated in clinical situations involving immunocompetent or a generally healthy patient for a small localized swelling in the absence of systemic signs and symptoms of infection or rapidly spreading cellulitis. (Table 2).

The recommendation for management of soft tissue edema of odontogenic origin includes clinical intervention in the form of incision and drainage. A rapid, sharp incision through the oral mucosa adjacent to the alveolar bone usually is sufficient to help rid the body of toxic purulent material and decompress the tissues. This technique allows better perfusion of blood containing defensive elements and increased oxygenation to the infected area.

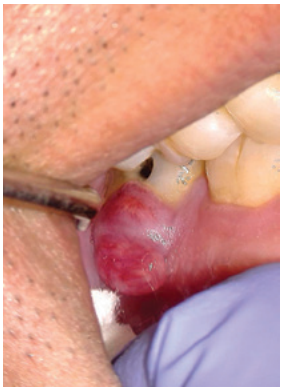

Figure 1: Tooth #31: Necrotic pulp/acute apical abscess, spreading infection

If the swelling is increasing in size or associated with cellulitis, antibiotics can be deemed necessary in addition to incision and drainage (Figure 1). This therapeutic combination will improve delivery of a minimum inhibitory concentration of the antibiotic to the area. Additionally, drainage from the canal decreases postoperative discomfort as well (15). Although, effective comprehensive treatment of endodontic infections must still include chemomechanical debridement of the root canal system, with the goal being the removal of the source of infection.

In one well-designed clinical trial exploring the effect of penicillin on patients with postoperative pain and swelling in symptomatic necrotic teeth, researchers reported that a prescription of penicillin postoperatively did not significantly reduce pain, percussion pain, swelling or the number of analgesic medications taken (16).

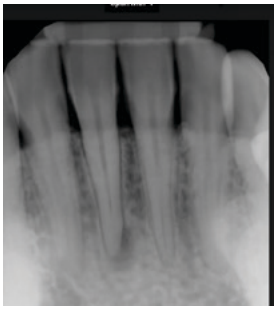

Figure 2: Tooth #25: Necrotic pulp/asymptomatic apical periodontitis, periapical radiolucency

Similarly, asymptomatic apical periodontitis of pulpal origin does not routinely require systemic antibiotic therapy for satisfactory resolution and healing (Figure 2). Endodontic therapy alone is usually sufficient to manage this clinical presentation. Although, for adult patients with pulp necrosis and symptomatic apical periodontitis, a delayed prescription should be provided if pulpotomy, pulpectomy, nonsurgical root canal treatment, or incision and drainage of the abscess is *not* immediately available for same day care (17).

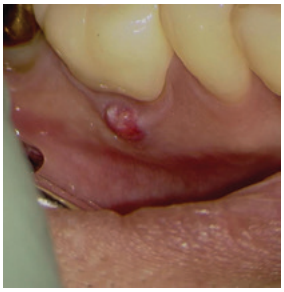

Figure 3: Tooth #30: Necrotic pulp/chronic apical abscess, sinus tract

When the intraradicular infection is able to overwhelm the host's immune response, viable bacteria are able to gain access to the periapical tissues and form an active infection. This results in the development of an apical abscess. A *chronic* apical abscess usually presents with gradual onset, none to mild symptoms and the presence of a sinus tract or parulis (Figure 3). The majority of chronic apical abscesses of endodontic origin do not require systemic antibiotic therapy for satisfactory resolution and healing (18). Systemic clinical manifestations of endodontic infections are best managed with a suitable regimen of systemic antibiotics (oral or IV) and when achievable, incision and drainage. Surgical incision and drainage is recommended to further reduce bacteria in the apical tissues. If the infection is actively draining, the endodontic access may be left open until the next day or a drain placed in the incision and left in place for 24-48 hours (19). When a patient presents with a rapidly spreading cellulitis or an infection with systemic involvement, more stringent infection

management protocols may include pulp space debridement, placement of an intracanal medication like calcium hydroxide and multiple appointments. Many studies have shown the importance of intracanal medication between sessions in order to kill microorganisms that biomechanical preparations are unable to address (20). Intracanal medications act beyond the root canal lumen, inside dentinal tubules and apical resorptions. The slow-working antibacterial properties of $Ca(OH)_2$ are attributed to its alkalinity and its ability to disrupt the cytoplasmic membrane, denature bacterial proteins and damage bacterial DNA (21).

Antibiotics

The literature provides no substantial evidence supporting the use of antibiotics to treat a periapical abscess, irreversible pulpitis, or symptomatic apical periodontitis. These are clinical manifestations which are treated effectively through drainage by means of pulpectomy, incision, or local debridement; hence antibiotics should not be prescribed. Before starting patients on antibiotic therapy, dentists need to consider various factors to determine the benefit-to-risk ratio. These include: the clinical diagnosis, the patient's medical and oral health status, the patient's current medication, and results of microbiological analysis, where feasible. When prescribing, dentists should use the shortest effective course of a narrow-spectrum antibiotic (22). The dentist should monitor the patient closely throughout the duration of the prescription. Amoxicillin and penicillin VK should be the first line of therapeutic antibiotics dentists prescribe to patients without a penicillin allergy (23). Amoxicillin in combination with clavulanic acid is effective for patients who continue to have an unresolved or recalcitrant infection after the treatment with a β-lactam such as penicillin VK but should not be used without prudent discretion because this combination can produce adverse effects such as gastrointestinal and hepatic disturbances (24). Documentation within the dental literature finds diarrhea as one of the more common side effects due to disruption of the normal gastrointestinal flora when antibiotic therapy is employed. Reports of antibiotic-associated colitis (AAC) and of pseudomembranous colitis in patients treated with antimicrobial agents have been noted, and are a significant concern (25).

Dentists should use metronidazole only to treat odontogenic infections when in combination with a penicillin because this combination provides excellent gram-positive and gram-negative coverage. For patients with an allergy to penicillin, clindamycin was the antibiotic of choice; however, because of the risk of colitis and the accompanying black box warning for clostridium difficile associated diarrhea which can be fatal, the dentist should first consider Azithromycin (26).

Antibacterial Drug resistance

Systemic antibiotics and their benefits in combating bacteria and infection also carry risk of morphing the same bacteria they are primed to target into "super bugs" that resist the therapeutic effects of the drug. The rate at which bacteria develop resistance to antibacterial drugs is alarming, demonstrating resistance soon after new drugs have been introduced. This rapid development of resistance has contributed significantly to the morbidity and mortality of infectious diseases. Antibiotic resistant infections account for 23,000 deaths and billions of dollars in excess spending in the United States annually (27). The concern of antibacterial resistance is not the antibiotics themselves as they remain an essential tool in modern health care characterized as one of the most predictable and readily available weapons against diseases. Instead, the problem is in the way the drugs are used. The inappropriate overuse of antibiotics has resulted in a crisis situation due to bacterial mutations developing resistant strains.

Table 3. Recommended antibiotics and dosages in endodontics

DRUG OF CHOICE	INITIAL DOSE *****Conditional recommendation*	ADULT MAINTENANCE DOSE
Amoxicillin w/ clavulanic acid	1000 mg 1000 mg	500 mg q8 h 3-7 days 500/125 mg q8h 7 days
Penicillin VK	1000 mg	500 mg q4-6 h 3-7 days
Azithromycin **Penicillin allergy w/ hx of hives, angioedema, or anaphylaxis*	500 mg	250 mg q24h (5 days including loading dose)
Cephalosporins (Cephalexin) **Penicillin allergy w/o hx of hives, angioedema, or anaphylaxis*	1000 mg	500 mg q6h 3-7 days
Clindamycin **Penicillin allergy w/ hx of hives, angioedema, or anaphylaxis*	600 mg	300 mg q6 h 3-7 days
Metronidazole ***Complement antibiotic*	1000 mg	500 mg q8h 5-7 days
Erythromycin ****Historical Antibiotic*	500 mg	250 mg q4-6h 7-10 days
Ciprofloxacin	500 mg	250-500 mg q6h x 7-10 days

**comparative safety and effectiveness of common antibiotics with Penicillin* ****essentially not effective against anaerobic* ***Provides great gram-negative anaerobic activity* *****Facility specific recommendations*

Early manifestations of bacterial adaptability to antibiotics were noted shortly after the introduction of penicillin G. Certain strains of *E. coli* and *S. aureus* produced penicillinase, a bacterial enzyme with an adaptive mechanism aimed at surviving exposure to the bactericidal agent. With this adaptation, the bacteria had acquired resistance to penicillin G (28). Penicillinase was capable of inactivating a core

structural component (the beta-lactam ring) of the antibiotic. Presently, the majority of *S. aureus* strains are resistant to penicillin G, including many resistant to later generation beta-lactamase-resistant penicillins. Whatever does not kill pathogenic microorganisms can make them stronger and more difficult to destroy later. Investigation of how acquired resistance develops has been a major focus of chemotherapy research since the early demonstrations of penicillinases (29). It is important to note that even as more sophisticated techniques are used to investigate specific genetic alterations and stable passage of nucleic acid segments between microorganisms, decades of accumulated scientific information continues to reinforce a few basic trends. Bacteria eventually develop resistance to every new antibiotic. Acquisition and the extent of resistance is a matter of degree. Selective pressure is exerted on microbial populations by antimicrobials. Early spontaneous mutations provide survivors with a growth advantage over susceptible targeted members of the population.

In 2013, a *Journal of the American Dental Association* publication looked at the prescribing for U.S. dentists according to antibiotic agent and category, patient demographic characteristics, and geographic region. In the United States, an overall prescribing rate of 77.5 prescriptions per 1,000 people was calculated (30). They noted the primary driver of antibiotic resistance is the use of antibiotics whether appropriate or inappropriate. The study concluded persistent efforts to combat antibiotic resistance will require all prescribers, including dentists, to examine prescribing behaviors for appropriateness and the effectiveness of guidelines to identify opportunities to optimize antibiotic use (Table 3).

Antibiotics for Consideration

Penicillin:

Treatment for odontogenic infections emphasizes penicillin as a first line of defense when managing dental infections. Penicillin VK has good effectiveness, low toxicity, as well as low cost. Penicillins inhibit cross-linking in the bacterial cell wall and are, thus, bactericidal. They have a fairly narrow antimicrobial spectrum, but cover most bacteria associated with odontogenic infections. In culture and sensitivity testing on 94 patients with odontogenic abscesses, penicillin V was the least effective antibiotic for eradicating bacterial isolates. Despite this, more than 95% of patients treated with surgical incision and drainage in conjunction with penicillin V recovered satisfactorily. A loading dose of 1,000 mg of penicillin VK should be orally administered, followed by 500 mg every four to six hours for three to seven days (31).

Amoxicillin:

Amoxicillin has a broader spectrum of activity than penicillin V. It does not provide any better coverage in treating odontogenic infections, yet tends to be more effective against various gram-negative anaerobes. It has an oral dosage of 1,000 mg loading dose with 500 mg recommended dosing every eight hours for 3 to seven days. Its dosing schedule and ability to be taken with food may make it more acceptable for patients, resulting in better compliance. Amoxicillin is also the antibiotic of choice for antibiotic prophylaxis of patients that are medically compromised (32). It has an extended spectrum which lends to resistant strains of microbes.

Cephalosporins:

The mechanism of action of cephalosporins is similar to that of penicillins. There are four generations of cephalosporins; their spectrum of antibacterial coverage, especially against gram-negative bacteria, generally increases from the first to the fourth generation. The reported incidence of cross-reactivity with penicillin is about 7-18% which should be considered when a patient reports an allergy to penicillin (33). Cephalosporins are not a first-line treatment in the management of odontogenic infections; however, they should be considered when there is not a true allergy to penicillin. Cephalexin is more commonly used for sinus communications and for antibiotic prophylaxis in patients with prosthetic joints.

Metronidazole:

Metronidazole is a synthetic antibiotic that is effective against anaerobic bacteria. It disrupts bacterial DNA, thus inhibiting nucleic acid synthesis. It provides excellent anaerobic coverage and should be used in conjunction with penicillin. If after the initial treatment symptoms do not improve over a two- to three-day period then metronidazole may be added to the original prescription of penicillin or clindamycin, with continuation of both antibiotics until completion. Embedded within its synthetic makeup is strong bactericidal activity against anaerobes. The lack of efficacy against aerobes and facultative anaerobes is a limitation in addition to a marked resistance of many bacteria (8). Usual dosage follows a 1,000 mg loading dose and 500 mg every six hours for five to seven days.

Clindamycin:

Clindamycin inhibits bacterial protein synthesis, making it bacteriostatic and bactericidal at high dosages. Its use has increased in recent years due to increasing concern over penicillin resistance, and as a viable option was the primary antibiotic of choice for patients with antibiotic allergy to penicillin (6). Clindamycin substantially increases the risk of developing *Clostridioides difficile*

infection even after a single dose, carrying a black box warning for *Clostridioides difficile* infection, which can be fatal (35). Clindamycin has excellent coverage of gram-positive cocci and anaerobic bacteria providing strong results in treating infections of odontogenic origin (34). A recommended choice if a change in antibiotic is warranted, it reaches a similar plasma level as that in bone due to the ability to be well distributed through body tissues. Eikenella is inherently resistant to clindamycin and alternative antibiotics should be considered if this species is found to be the causative organism. Clindamycin should be prescribed with a 600 mg loading dose followed by 300 mg dosing every six hours for five to seven days.

Macrolides:

In dentistry, erythromycin is a macrolide with infrequent use in dentistry. Once prescribed as an alternative to patients with a penicillin allergy due to its spectrum of activity similar to that of penicillin V. Like penicillin-resistance, efficacy of erythromycin has become a clinical concern. Kuriyama and colleagues found that erythromycin was ineffective against *Streptococcus viridans* and most Fusobacterium species and essentially not effective against anaerobic bacteria (36). Thus, erythromycin should be considered a historical antibiotic in the management of odontogenic infections.

Azithromycin:

Azithromycin is effective against a variety of aerobic and anaerobic gram-positive and gram-negative bacteria with improved pharmacokinetics (37). For patients with a true allergy to penicillin, the primary alternative antibiotic recommendation has changed. It is now azithromycin with a loading dose of 500 mg, and then 250 mg for four additional days (17). Azithromycin may see absorption inhibition with food and heavy metal consumption and bacterial resistance rates for Azithromycin that are higher than for other antibiotics (38). Close monitoring of patients who receive Azithromycin is recommended and patients should notify a healthcare provider should their infection worsen while on therapy.

Flouroquinolones:

Fluoroquinolones include the antibiotic ciprofloxacin which interferes with bacterial DNA metabolism by inhibiting the enzyme topoisomerase which promotes replication. It is not effective against anaerobic bacteria usually found in endodontic infections (39). It should be considered as a second line therapy to penicillin V, metronidazole and clindamycin if an infection is persistent and bacterial culture shows bacterial susceptibility.

Conclusion

Odontogenic infections are polymicrobial in nature. Astute diagnosis with appropriate treatment, including elimination of the causative factor, is crucial for successful management of dental infections. Antibiotics are a useful *adjunct* in the treatment of odontogenic infections, but should not replace removal of the etiologic agent (40). Identifying factors contributing to antibiotic resistance through the use and abuse of these drugs is paramount. All dentists should know if and when to prescribe antibiotics and the respectable time for referral to a specialist. Prudent antibiotic stewardship needs to be embraced by the dental community with prescribing patterns reflective of current best habits and practices.

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Exclusive Online Bonus Materials: AAE Antibiotic Prophylaxis 2017 Update

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180 N. Stetson Ave. Suite 1500
Chicago, IL 60601
Phone: 800-872-3636 (U.S., Canada, Mexico)
or 312-266-7255
Fax: 866-451-9020 (U.S., Canada, Mexico)
or 312-266-9867
Email: info@aae.org

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