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Antibiotic therapy—managing odontogenic infections

James Q. Swift, DDS[a,*], Wendy S. Gulden, DDS, MS[b]

[a]*Oral and Maxillofacial Surgery, Department of Diagnostic and Surgical Sciences, University of Minnesota School of Dentistry, 515 Delaware Street Southeast, 7-174C Moos T, Minneapolis, MN 55455, USA*

[b]*Department of Restorative Sciences—Endodontics, University of Minnesota School of Dentistry, Minneapolis, MN 55455, USA*

Several pharmaceuticals have been developed in the past 10 years that have made a significant impact on the health of the human race. There have been few advances, however, that have proved more efficacious than the pharmacotherapies we have had available for many decades for the treatment of odontogenic infections. Many new antibiotics/antimicrobials have been developed, but none have been determined to be of significant benefit to replace or supplant the use of penicillins for the management of orofacial infections caused by pathogens in and around the oral cavity. Judicious use of antibiotics in conjunction with surgical therapy is the most appropriate method to treat odontogenic infections. Using the antibiotic "du jour," many times promoted by pharmaceutical representatives, results in costly and unnecessary complexity of care. A return to the basics is indicated for the antibiotic management of odontogenic infections.

Chemotherapy is defined as the use of synthetic, semi-synthetic, and naturally occurring chemicals that selectively inhibit specific organisms causing disease. The term antibiotic means "against life" (*anti* = against and *biosis* = life).

The decision to use an antimicrobial/antibiotic agent in managing an odontogenic infection is based on several factors. The clinician must first diagnose the cause of the infection and determine the appropriate dental treatment that may include multiple modalities, including initiation of endodontic therapy and pulpectomy, odontectomy, or surgical or mechanical disruption of the infectious environment. The determination as to whether

* Corresponding author.
E-mail address: swift001@umn.edu (J.Q. Swift).

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conjunctive antibiotic therapy is indicated is based on several factors, including host defense mechanisms, severity of the infection, magnitude of the extension of the infection, and expected pathogen. Because of the lack of circulation within dental pulp, the normal host defenses (inflammation and immunity) are compromised and the root canal system becomes a unique environment to harbor a limited group of bacteria.

Most odontogenic infections are polymicrobial and are composed of at least two predominating bacteria [1]. Most bacteria comprising the oral flora are nonpathogenic and have not been shown to proliferate and grow in host tissue [1]. When the dental pulp is overwhelmed from the bacterial attack, a local acute inflammatory response is seen, followed by nonspecific and specific immunologic reactions with the presence of lymphocytes, plasma cells, and macrophages. Eventually polymorphonuclear lymphocytes (PMNs) are chemotactically attracted to the area of damaged tissue. An abscess, a fibrocollagenous layer of tissue, may form around an accumulation of PMNs in the region of infection, isolating it from surrounding tissue. Because the host may be unable to resorb the abscess and resolve the infection, root canal treatment, extraction, or other surgical therapy is needed to remove the cause. Recent studies demonstrate that a localized abscess may be an inflammatory/immunologic phenomenon and in some patients represents a nonbacterial cause for the periapical localized clinical symptoms [2,3]. The effectiveness of an oral antibiotic as primary and sole treatment for an infection of odontogenic etiology is highly questionable because of the lack of effective circulation in a necrotic pulp system and an abscess. This concept reinforces the idea that surgery of some kind is the primary treatment of an infection of odontogenic source, and that antibiotic therapy is adjunctive care. Observations reveal that many clinicians, however, do treat odontogenic infections primarily with antibiotics, especially when there is a question as to the etiology of the symptoms of a potential infective process. Endorsement of a philosophy of care that antibiotic administration is low risk and potential high yield cannot be substantiated, especially with the current concern regarding bacteria that have developed resistance to current antibiotic therapy. Antibiotics should not be prescribed as a substitute for proper dental treatment.

Mechanism of action

Antibiotics have various effects on bacteria based on their pharmacologic action. The most commonly used antibiotics in dentistry (penicillins, cephalosporins, and vancomycin) work by attacking the cellular processes necessary for the bacterial cell wall synthesis while having no effect on host cells. Other commonly used antibiotics in dentistry exert their effect by inhibiting translation needed for bacterial protein synthesis (erythromycins, tetracyclines, aminoglycosides, and chloramphenicol). Metronidazole, indicated

in dentistry for anaerobic bacterial infections, is a direct-acting agent that binds and degrades DNA in bacteria. Still other antibiotics (amphotericin B, polymixins) act by inhibiting cell membrane function. Further development in determining the difference between host and bacterial protein synthesis may lead to the development of alternative sensitive and specific antibiotic therapeutics.

The emergence of resistant bacteria is growing. The microbial ecosystem is engaged in trying to remain opportunistic and by mutating and adapting, resistant strains develop. Specific enzymes can destroy the antibiotic once it has entered the bacteria, permeability into the cell wall can become difficult, and an alteration of certain targets that the drug attaches to become apparent. Mutations in any of these functions can result in loss of sensitivity and specificity to any of the previously mentioned antibiotics.

New synthetic antibiotics for potential use in dental-related infections are the quinolones (cinoxacin, nalidixic acid, and methenamine) and the fluoroquinolones (ciprofloxacin, norfloxacin, and ofloxacin). These agents should be considered when culture results have revealed that these antibiotics are warranted. They have a broader spectrum of action and inhibit bacterial DNA replication (fluoroquinolones inhibit DNA gyrase that inhibits the uncoiling of DNA for replication). The limited indication and the high cost of these drugs is a serious consideration before prescribing. They are rarely used in the management of odontogenic infections.

Bacteria have two major advantages that allow them to survive and prosper in the host system. They replicate quickly and can produce multiple mutations spontaneously. Once a mutation is present, all bacteria offspring generally acquire the new trait. Genetic transfer is another process that bacteria possess. Genetic transfer allows families of bacteria to share desirable traits with a wide range of microbial species. It has recently been found that antibiotic-resistant genes can be passed among every species of bacteria.

Indications for the use of antibiotics

Clinical effectiveness in treating an infection is based on correct diagnosis. Once the source of the infection has been established, dental procedures should be used immediately to disrupt the microorganisms involved. Antibiotic therapy should be used as an adjunct to dental treatment and never used alone as the first line of care. Antibiotics are indicated when systemic signs of involvement are evident. Pain alone or localized swellings do not require antibiotic treatment. Fevers greater than 100° F, malaise, lymphadenopathy, or trismus are clinical signs that possible spread of the infection has occurred. A rapidly spreading infection or persistent infections are other indications for which one may prescribe an antibiotic. Clinicians should consider consulting a specialist if the swelling spreads to extraoral spaces or obstructs breathing or swallowing. The choice of an antibiotic should be based on knowledge of the usual causative microbe. The empiric approach usually results in favorable

outcomes [4,5]. Penicillin is the first choice in managing odontogenic infections because it is susceptible to gram-positive aerobes and intraoral anaerobes, organisms found in alveolar abscesses, periodontal abscesses, and necrotic pulps. Patients with compromised host defense systems may indicate antibiotic therapy in conjunction with their dental treatment. Organ transplant patients and patients with poorly controlled diabetes are two examples that point toward the use of antibiotic therapy.

Indications for culturing

Although culturing is rarely required in managing odontogenic infections, at times it is necessary to resolve a progressive infection. Culturing methods have improved over the years; however, one should keep in mind that a bias may occur during the isolation and culturing of bacteria. Many anaerobic microbes are killed quickly when exposed to oxygen. Needle aspiration techniques and transfer under inert gas should be used when culturing for aerobic and anaerobic bacteria in the oral cavity. The antibiotic is then chosen to treat the predominant microbe found in the culture if empiric therapy has failed. The following are indications for culturing an odontogenic infection.

1. The patient is not responding to the first antibiotic prescribed after 48 hours and appropriate dental treatment has been completed.
2. The infection is progressing to other facial spaces.
3. The patient is immunocompromised or has a history of bacterial endocarditis and is not responding to the antibiotic therapy.

Antibiotic treatment should begin immediately even when a culture is taken because of the rapid spread of oral infections.

Antibiotics of choice

Penicillin is still the gold standard in treating dental infections. Penicillin has contributed to a dramatic decrease in mortality in serious odontogenic infections such as Ludwig's angina and diffuse orofacial cellulitis [6]. Aerobic and anaerobic microorganisms are susceptible to penicillin [7]. Pen VK is the obvious choice over Pen G because of the greater oral absorption by Pen VK. Pen VK is bactericidal and active against replicating bacteria often encountered in odontogenic infections [8]. The side effect encountered most often in penicillin is hypersensitivity, which is found in roughly 3–5% of the population. Certain bacteria can develop resistance to the penicillins because of the B-lactamase enzymes that inactivate the penicillin. A combination antibiotic consisting of a penicillin and clavulanic acid, a B-lactamase inhibitor, or the use of clindamycin, an antibiotic specific for infections caused by staphylococci, streptococci, pneumococci, and other bacterial species may be necessary in an infection not responding to penicillin alone. Cephalexin, cephradine, or cephadroxil, all first generation cephalosporins, provide a slightly broader antibiotic spectrum, especially when gram-positive organisms are suspected

to be the cause of the infection being treated. Cephalosporins beyond the first generation are not indicated in most odontogenic infections.

If an antibiotic is warranted, providing adequate blood levels is essential. A loading dose of 2000 mg Pen VK approximately 1 hour before beginning surgical therapy followed by 500 mg every 6 hours for 5–7 days is optimal. If the infectious signs and symptoms continue beyond 5–7 days, additional antibiotic therapy may be indicated. If within 48 hours the patient is not responding to penicillin, one could consider adding metronidazole. It is prescribed in a 500-mg dose every 8 hours for the duration of the antibiotic therapy. Metronidazole is active only against obligate anaerobic bacteria by penetrating all bacterial cells and inhibiting DNA replication. It should not be used in pregnant patients or patients with a history of seizures, and if combined with ethyl alcohol can produce nausea and vomiting. Another alternative to treat an infection that is not responding to penicillin is clindamycin. It may be used as a first-line antibiotic if the infection is deemed to be more mature and potentially has spread to bone. Indiscriminate use should be avoided (see later discussion). A loading dose of 600 mg may be administered approximately 1 hour before surgical therapy begins, followed with 300 mg every 6 hours for the duration of the infection (5–7 days).

Appropriate diagnosis and surgical therapy coupled with the empiric use of antibiotics and sound clinical judgment in assessing improvement is the standard of care in the management of odontogenic infections

Antibiotic preparations for odontogenic infections for adults

Pen VK 500 mg every 6 hours, tablets: 125 mg, 250 mg, and 500 mg
Amoxicillin 500 mg every 8 hours, tablets: 250 mg
Metronidazole 500 mg every 8 hours, tablets: 250 mg and 500 mg
Clindamycin 150–300 mg every 6 hours, capsules: 75 mg and 150 mg

Myths

There are many myths that pervade the clinical practice of dentists regarding the diagnosis and management of odontogenic infections. These behaviors have been observed repeatedly in the course of clinical practice. To dispel the continued improper use of antibiotics in the dental environment, these myths are exposed in this discussion.

Myth #1: antibiotics are not harmful

The unwarranted administration of antibiotics is not without risk. The risks for pseudomembranous colitis and allergic reaction must be taken into consideration before prescribing.

Many antibiotics can disturb the normal microbial flora of the gastrointestinal tract, which may cause severe diarrhea and potentially fatal pseudomembranous colitis. These reactions occur more frequently when using oral administration of antibiotics versus parenteral administration,

based on variation of hepatic circulation of the drug associated with the two mechanisms of administration. Various degrees of allergic responses have been reported with the use of common antibiotics used for odontogenic infections. Dermatologic reactions such as rash or hives represent milder reactions, whereas life-threatening anaphylactoid reactions have occurred. It has been estimated that 100–300 fatal allergic reactions to penicillin occur annually in the United States [9,10]. For an allergic reaction to have occurred, previous exposure to the drug is necessary. This may have occurred by the patient receiving the antibiotic in beef, milk, or poultry products where the uncontrolled use leaves a residue of the antibiotic in food products [11]. It has been estimated when given amoxicillin that 1 in every 10 patients develops a rash, 1 in every 10,000 develops anaphylactic reactions, and 1 in every 100,000 dies from an allergic reaction [12–14]. Two types of allergic reactions can arise. An acute allergic response or an anaphylactic reaction occurs within 30 minutes of receiving the drug and the reactions include bronchoconstriction, urticaria, angioedema, and shock. Treatment of this type of reaction involves the administration of epinephrine, antihistamine, and possible corticosteroids. Delayed allergic responses take longer than 2 hours to develop and demonstrate mild skin rashes, glossitis, and local inflammatory reactions. Therefore, antibiotic therapy should not be prescribed unless justification for the need is warranted. The improper use of antibiotics can cause the patient serious adverse effects. It is the clinician's responsibility to determine the benefit:risk ratio before administrating the antibiotic.

Myth #2: doses and duration of antibiotic treatment should be nonspecific and variable for most odontogenic infections

Inappropriate dosing of an antibiotic can result in inadequate concentration of the drug at the site of the infection. This practice can promote recurrence of infections and development of resistant bacterial strains. As vulnerable microorganisms die, the number of surviving microbes increases, making each successive bacterial generation better equipped to resist future antibiotic challenges. This selection process accelerates when the drugs are administered in doses small enough to allow stronger bacteria to survive the antibiotic assault. Eventually, strains of bacteria are created that can resist antibiotic therapy. In an average size patient with an odontogenic infection serious enough to warrant antibiotic therapy, there is little indication for the use of doses of penicillin as low as 250 mg. Five hundred mg of penicillin is the lowest dose that should be prescribed for an adult. Inadequate duration of the therapy or overdosing of the antibiotic can also result in damaging the host response and producing toxic effects. A rule of thumb when prescribing is that the antibiotic should last for 3 days after the patient's symptoms have resolved. Treatment of most odontogenic infections requires an average of 5–7 days of therapy; however, treatment of severe infections or immunocompromised patients' therapy may be of longer duration.

Patient compliance is another complication in effective treatment. The drug may be too expensive or not covered by a third party payer and the prescription remains unfilled. Dosing frequency may be complicated. The compliance issue most often observed is missed doses after clinical symptoms have subsided. Another challenge to compliance is the untoward or unexpected side effects that can occur when taking antibiotics. In all these cases, mutated microbes can flourish and cause serious consequences.

Myth #3: antibiotics are always indicated when treating dental pain (odontalgia)

Irreversible pulpitis is a result of severe inflammation of the pulp system. A large quantity of inflammatory mediators and neuropeptides are present, which results in vascular permeability and elevated capillary pressure. Because of the hard tissue in which the pulp is encased and its low-compliance environment, the pulp is unable to neutralize these mediators. Pain is often caused by the release of these mediators that lower pain thresholds and causes spontaneous firing of sensory nerves. Pain of irreversible pulpitis may be sharp, dull, localized, or diffuse, and may last minutes to days. Chemomechanical removal of the pulpal tissue is the treatment of choice. An old but often popular idea was the use of intracanal medicaments to help alleviate the patient's pain complaint. This concept can be dismissed as it is ineffectual. Cleaning and shaping of the root canal with the use of sodium hypochlorite, a dry cotton pellet, and temporization of the access is the desired treatment [15]. Odontectomy may be indicated if the tooth is deemed to be nonrestorable. Appropriate analgesics may be indicated but antibiotics are not. The patient's condition should improve rapidly once the source of the infection is eliminated. If the problem persists, consultation with a specialist may be warranted.

Myth #4: clindamycin is a first line drug for infections

Clindamycin is an antimicrobial reserved for anaerobic, later stage odontogenic infections. It exhibits bacteriostatic activity, thereby inhibiting protein synthesis. Clindamycin should be considered only as the first line of choice if the patient has had an allergic reaction to penicillin or if it can be determined that an osteomyelitis caused by anaerobic microbes is present [7]. It is an excellent choice for treating serious intraosseous infections. Clindamycin has less antigenic potential than penicillin, but has a slightly higher incidence of gastrointestinal adverse effects caused by the overgrowth of *Clostridium difficile* [16]. Recent studies show that colitis is a possible adverse effect of most antibiotics, especially broad-spectrum penicillins and cephalosporins. This condition is often observed in recently hospitalized elderly patients who have had previous abdominal complaints and received high doses of an antibiotic.

Myth #5: if a periapical radiolucency, sinus tract, fistula, or localized abscess is present, antibiotics are always indicated

A periapical radiolucency, sinus tract, or fistula indicates a necrotic pulp. A vital pulp cannot exist with any of these objective signs. Because there is

not significant vascularization to necrotic canals or abscesses, the effectiveness of antibiotic therapy is highly questionable. Therapeutic concentrations of an antibiotic at the site of the infectious process cannot be obtained. A localized abscess (swelling) begins from the necrotic debris in the root canal and diffuses into the surrounding bone at the apex of the tooth, resulting in a swelling or sinus tract formation.

Controlled clinical trials using penicillin, placebo, and neither medication in patients presenting with pulpal necrosis and periapical pain or localized swelling showed no differences between groups in the course of recovery or symptoms after debridement of the root canal system [17].

Local dental treatment is most important in resolving the infection. Root canal treatment or extraction if the tooth is not restorable accomplishes the removal of the irritants and drainage of the swelling. Incision and drainage is indicated if there is no drainage obtained from the tooth or tooth socket. Drainage helps in decreasing discomfort the patient is experiencing by releasing blood and serous fluids that contain bacteria and their byproducts. Intraoral drainage removes these local irritants and improves circulation.

Myth #6: antibiotics must be given for several days before implementation of surgical treatment

The polymicrobial environment of odontogenic infections persists until the source of the irritation is removed. Dental treatment establishes a favorable environment to the host to alleviate the disease. The key to successful resolution of the infection is initial drainage of the infection coupled with either thorough chemo-mechanical debridement of the root canal system or extraction of the tooth or as an emergency measure until such time that definitive dental therapy can be implemented. The vast majority of localized odontogenic infections can be successfully treated by appropriate dental treatment alone. Medically compromised patients who present with dental pain, sinus tracts, radiolucencies, apical periodontitis, or localized intraoral swellings do not routinely require antibiotics [17]. It is appropriate however to administer oral antibiotics approximately 1 hour before surgical therapy is initiated as the surgical therapy disrupts vascular supply to the infected area. Some antibiotic is delivered to the areas approximating the infection where tissues are minimally affected by the infection. Any time differential greater than 1 hour between administration of oral antibiotic and surgical therapy is not warranted. If the antibiotic is administered parenterally, tissue levels adjacent to the infection are established in much less than 1 hour.

Myth #7: indurated soft tissues means drainage is not indicated

The clinician need not wait until a swelling become soft or fluctuant before incising and draining. Diffuse fluctuant or indurated soft tissues are a more severe manifestation of the localized abscess. Surgical therapy (root canal treatment or extraction) is indicated primarily if the etiology is a necrotic tooth. If adequate drainage is not accomplished, soft tissue incision

and drainage may be indicated. If soft tissue swellings (cellulitis) are left untreated, infection can spread to adjacent facial spaces resulting in serious consequences such as airway compromise, sepsis, blindness, mediastinal involvement, and death. Fluctuant swellings usually emit purulence immediately when incised, whereas a more indurated swelling results in small quantities of blood and serous fluid. Draining both types of swellings releases pressure from the area and facilitates good recovery by providing oxygen to an anaerobic environment, increasing blood circulation, and thereby optimizing host defense mechanisms. A culture and sensitivity should be obtained when draining an infection, not to guide the initial antibiotic selection, but to be available should the empiric antibiotic therapy used fail.

Myth #8: overprescription of antibiotic therapy does not occur in dentistry

Overuse and improper use of prescription drugs by dentists has been well documented. The national Centers for Disease Control and Prevention estimate that approximately one third of all outpatient antibiotic prescriptions are unnecessary. Nearly $23 billion worldwide has been spent on antibiotics in the last year [11]. Approximately 10% of antibiotics are now rendered ineffective [11]. The patient who demands to leave the appointment with a prescription in hand may drive the misuse of antibiotics. The reality is that appropriate dental treatment, analgesic therapy, and education of the patient will alleviate the patient's symptoms and build trust in the doctor–patient relationship.

A step-by-step approach for diagnosing and treating odontogenic infections

1. Listen to the chief complaint of the patient. This is the symptom that the patient is experiencing and describes in his or her own words.
2. Take a comprehensive health history. Review systemic diseases, past surgeries, injuries, and medications the patient is taking. Review any allergic responses a patient may have experienced.
3. Obtain a thorough dental history of existing problems: When did the problem begin, is it getting worse or better, and what medications is the patient taking for it?
4. Extraoral and intraoral examination for the presence and extent of pathosis. Percussion, palpation, and pulp vitality testing are indicated to diagnose pulpal and periodontal disease.
5. Radiographic examination is an adjunct in determining dental disease. Most pathologic states in pulpal tissue are not visible on a radiograph. Only when the cortical plate has been resorbed does the dental radiograph become helpful in identifying disease.
6. Treatment planning is discussed with the patient once the nature of the pathosis has been identified. Determine the difficulty of the case and whether handling it is within your comfort level or if the case should be referred. The clinician should calculate a prognosis for each case

including a contingency prognosis if problems are encountered after treatment has begun.
7. Designing the appropriate dental treatment should be rendered: emergency and definitive treatment.
8. Case selection completed and referral to a specialist if found that the patient's needs are beyond the capacity of the clinician's capabilities.
9. Appropriate analgesics and postoperative instructions given.
10. Selection of an antibiotic if warranted:
    a) Choose the narrowest spectrum antibiotic possible to prevent disturbing the host's normal microbial flora.
    b) Prescribe the medication with the appropriate dose and duration.
    c) Educate the patient about the importance of taking the medication for the proper length of the time.
    c) Provide adequate analgesic therapy along with antibiotic therapy if the patient is also experiencing pain.
    e) Closely monitor the patient and follow up in 48 hours to make sure the dental treatment and antibiotic therapies have reduced the patient's symptoms. If there has not been a reduction in symptoms, consider adding another antibiotic, culturing the infection, or referring the patient to a specialist.

New developments

Advances in science and molecular developments in studying bacterial function may help researchers "customize" future antibiotics to kill certain bacteria. New technologic advancements, such as radiographic crystallography, that help in studying the enzymes that promote drug resistance are advances that help control antibiotic resistance in humans. Genetics is yet another promising avenue for exploring bacterial functions.

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