Review Article

Pattern of antibiotic prescription for orofacial infections among dentists: A systematic review of the literature

Abstract:

Bacterial infections are common in dental and oral clinical practice. It is been estimated that about 10% of total antibiotic prescriptions are related to dental infections. Combination of amoxicillin-clavulanate and plain amoxycillin is the most commonly used drug by dentists across the world. Three general considerations were recognized in this literature review—Empirical antibiotic prescription by dentists without a culture test; concomitant prescription of antibiotics with non-steroidal anti-inflammatory drugs which may ultimately affect the bioavailability of the former drug; and the increased antimicrobial resistance amongst oral pathogens. Since decades, antibiotics have been prescribed for the treatment of odontogenic infections and non-odontogenic oral infections, and for focal infections and sepsis prophylaxis. Renal failure, liver failure, and pregnancy are situations that require special attention when considering an antibiotic prescription. This review attempted to contribute to the rational use and abuse of antibiotics while focusing on the general characteristics of these drugs.

Keywords: Antibiotic, prescribing pattern, Odontogenic infections, treatment, prophylaxis.

Introduction

The oral cavity normally houses a complex population of microorganisms. Occurring odontogenic infections are also polymicrobial in nature. However, almost all of the times, such infections are predisposed by anaerobic bacteria. Thus, to treat such infections or prevent their occurrence, antibiotics have been always prescribed by attending dentists. These drugs were typically introduced into the market in the mid-twentieth century, in the early 1900s, in the form of sulfa drugs that were later followed with the discovery of penicillin, tetracyclines, and erythromycin. Clearly, the correct use of antibiotics offers many benefits including the resolution of infections, prevention of the spread of disease and minimization of serious complications of disease.

However, the use of antibiotics is not totally safe as it can cause nausea, vomiting, diarrhea, and stomach cramps because of the disturbances of the gut microflora. A particular concern associated with the use of oral antibiotics is the development of clostridium difficile infection. This is especially true with clindamycin, amoxicillin, and cephalosporins that are commonly prescribed for endodontic infections (1). Other antibiotics predisposing for clostridium difficile, such as macrolides and metronidazole, are less commonly used in dental practice (1). It is worth mentioning that this secondary infection was responsible for around half a million reported infections in the United States and was associated with around 29,000 deaths in 2011 (2). Other side effects associated with the use of antibiotics include the development of oral or vaginal yeast infections due to an imbalance in the body's normal flora. Other less common side effects include—allergic reactions which range from mild rash to more complicated skin reactions (i.e., Stevens-Johnson syndrome) and anaphylaxis.

Moreover, the overuse or misuse of antibiotics are creating health alarm as resistant bacteria, that lack susceptibility to any of the present antibiotics, are becoming more evident (3). Unfortunately, according to a recent report released by Ventola, it was found that up to 50% of all antibiotics prescriptions were prescribed for a wrong indication (3). He research has been registered in research center of research center of Riyadh elm university with IRB number FIRP/2020/65/243/239.

Debridement and drainage prior to antibiotic administration

A key consideration for the successful management of orofacial and endodontic infections is the adequate debridement of the infected area to adequately remove all pathogens and their byproducts and surgical drainage for both soft and hard tissue prior to the administration of antibiotics which favors the lesion's resolution. In such cases, broad spectrum antibiotics should be avoided and more effective and specific ones should be used for the shortest duration possible with close monitoring. However, the administration of antibiotics may not always be favored as it does not offer additional benefit; that is, abolishing signs and symptoms of already debrided or drained irreversible pulpitis, symptomatic apical periodontitis, or localized acute apical abscess (4-10). Additionally, according to more recent studies, it has been noted that the adjunctive administration of antibiotics is ineffective with adequate debridement and drainage in cases of localized orofacial infections (4-7). For spreading infections or non-feasibility of debridement at the time of presentation, there is also inadequate evidence about the indications, effectiveness, and the sufficient duration of medication administration. More importantly, ethical considerations limit the implementation or the ideal design of further studies that backs up the use of antibiotics in these cases. Available studies are subject to

bias; thus, they do not offer solid evidence that support their prescription (11-13). Several available studies report the routine prescription of antibiotics among dentists for dental pain (14,15) which tend to resolve due to a strong placebo effect (16). Yet, other dentists prefer to educate their patients about the signs and symptoms of worsened and spreading infection that necessitate the use a "stand-by" antibiotic prescription. Other controversial case scenarios that a dentist may encounter include the prophylactic use of antibiotics in cases as the prevention of late prosthetic joint infection following a dental work where there is little evidence about its efficacy. Overall, the benefits and risks associated with the of antibiotics should be well weighed before the prescribing decision taken by dentists.

For successful eradication of the pathogen, it is necessary to reach the minimal inhibitory concentration (MIC) of the drug against this sensitive microorganisms at the infection site. However, in cases of severe endodontic infections, tissue vascularization may be altered following dental pulp necrosis which limits the use of orally administered drugs whose distribution may be limited to surrounding vascularized tissues. Similarly, the pus, relating to apical abscess, limits the blood flow and drug distribution, and the cellular debris bind the free drug which necessitates adequate drainage and debridement (17).

Antibiotics indications in dental practice

The use of antibiotic should therefore be indicated as a supplementary therapy whenever any of the systemic signs of infection are present (i.e., fever, malaise, or lymphadenopathies) and only after the disinfection and drainage of the infection site (7,18). A prophylactic antibiotic course should be also indicated for less immune-protected individuals or patients at risk (endocarditis and joint prostheses) and as

prophylaxis against local infection and systemic spread in oral surgery. Conditions not falling into one of the preceding categories have no solid evidence for an established benefit following the use of antibiotics (3).

Treatment of acute odontogenic infection

In a consensus written by Bascones et al. (19), it was suggested that antibiotics be administered for odontogenic infection of pulp origin as a complement to root canal treatment, in ulcerative necrotizing gingivitis, in periapical abscesses, in aggressive periodontitis, and in severe infections of the fascial layers and deep tissues of the head and neck. However, in case of chronic gingivitis or periodontal abscesses (except in the presence of dissemination) initiation of antibiotics was not recommended. Although they agreed on the use of beta lactam, no specific drug belonging to this class was preferred over the other.

Choice of antibiotics and their dosage and duration

For therapeutic indications, antibiotics are usually chosen empirically with a predefined empirical dosage and duration. Globally, beta-lactam antibiotics (i.e., penicillin and amoxicillin), which bind to and inhibit penicillin binding proteins (PBP), are the preferred option in dental practice (20,22). Indeed, bacterial resistance to amoxicillin with clavulanic acid is very uncommon (23-26). PBP are essential for peptidoglycan cell wall synthesis and their inhibition results in bactericidal effect in both gram-positive and gram-negative bacteria (27). Infected root canals often include facultative and obligate anaerobes which are susceptible to this class of medications (23,24,28,29).

Nevertheless, allergy to penicillin is very common as it is estimated that around 8% of the American population have allergy to penicillin (30). The most severe form of beta-lactam allergy is the anaphylactic reaction, yet they are the least prevalent (31).

Given the increased gastrointestinal (GI) absorption and the broader spectrum of amoxicillin compared to penicillin, the former has greater efficacy especially against certain gram-negative anaerobes and decreased risk for GI flora depletion and digestive problems respectively. Furthermore, the absorption of amoxicillin is not altered by food and the larger fraction of it remains unbound in blood and freely active. Additionally, the prolonged half-life of amoxicillin, that is taken 2-3 times daily, compared to penicillin, which should be administered 4 times daily offers better patient compliance (32,33). The regularly recommended dose of amoxicillin for adults is 500 mg three times daily with an optional 1000mg loading dose. However, there is no real consensus over the adequate duration of treatment which usually lays between 3 to 7 days (14,34). Shorter courses (i.e., 2-3 days) are usually preferred when used as an adjuvant therapy (35,36). On the flip side, longer courses (i.e., 7 to 10 days) are usually recommended by studies that treat infections of unknown etiology or the bloodstream infections in hospitalized patients. Increased resistance among bacterial strains is more likely to happen with therapies that are extended over 7 days or longer or with the medication's over-prescription (37). This is alarming as it is approximated that around 30% of severe dento-alveolar infections have penicillin resistant bacterial strains (38). Several resistance mechanisms have been evident against this class of antibiotics which include—increased expression of high molecular weight PBP of decreased affinity towards beta-lactam antibiotics; increased expression of beta-lactamase enzymes (i.e., penicillinase) and drug efflux pumps (38).

Thus, the addition of a beta-lactamase inhibitor (i.e., clavulanic acid; 125 mg bid or tid) to amoxicillin may be warranted for an ensured eradication of endodontic bacteria (23-25). This combination, however, can result in gastrointestinal and hepatic changes which limits its use (40).

In case of penicillin hypersensitivity, the lincosamide clindamycin is deemed a preferred option. This drug inhibits protein synthesis by binding to the 50S ribosomal subunit thus causing a bacteriostatic effect (41). Clindamycin is considered highly effective against the majority of endodontic pathogens which comprise both facultative and obligate anaerobes (24,25,42). The absorption of clindamycin is also not impacted by food consumption and the serum level is peaked (9 µg/ml) 1 hour after the oral administration of 600 mg loading dose in adults which is followed by 300 mg every 6 hours. The recommended dose in children is 10-30mg/Kg (dose/ body weight) to be divided into 4 equal doses. However, the use of clindamycin is associated with several adverse effects which can be accentuated with the prolonged use of the drug. Those side effects include the increased risk for secondary infection with clostridium difficile bacteria that may progress into more severe situation marked by the development of pseudomembranous colitis (43). The primary signs and symptoms of the aforementioned disease include—diarrhea with fever, abdominal cramps, hematochezia and mucus in the stool, which may warrant the drug discontinuation and referral into a primary care physician. Discussing this problem with the patient is essential where caution should be applied when the patient has a positive history for clindamycin-associated pseudomembranous colitis (44). In this case, other antibiotics (e.g., macrolides such as azithromycin, quinolones such as moxifloxacin, or tetracyclines) are considered a preferred option although they are less

effective against oral pathogens (23,41). Yet, other studies report the increased effectiveness of moxifloxacin and azithromycin over clindamycin (45,46).

Isla et al. suggested that amoxicillin-clavulanic acid, clindamycin and moxifloxacin are considered the antibiotics of choice for the treatment of odontogenic infections. They also reported that the combination of usual-dosage spiramycin-metronidazole fails to cover the full bacterial spectrum in this kind of infections. They also recommended clindamycin dose to be 300 mg/6 hours, and 500 mg/8 hours or 2000 mg/12 hours for amoxicillin-clavulanic acid (with 125 mg of clavulanate in both cases) (47).

Treatment failure

Local debridement along with appropriate antibiotic course may not always be effective dur to an infection with some variant species of virulent bacteria (i.e., multidrug resistant bacteria) or fungal infections. It is worth mentioning that antibiotics are useless for actinomycosis infection. Testing for the causative pathogen is especially advised for immunocompromised patients (e.g., patients infected with HIV or having uncontrolled diabetes), patients having penicillin allergy and those presenting with a history of C. difficile infection. Nevertheless, oral infections are polymicrobial in nature and almost half of oral pathogens are however non-cultivable. Furthermore, despite their storage in pre-reduced transport media (e.g., Liquid Dental Transport Medium), swab testing may prompt less accurate results due to the increased risk for contamination of anaerobes or their death. Generally, needle aspiration of the purulent fluid and direct lab testing is the preferred method for better identification of strict anaerobes (48). This practice is, however, subject to controversy as—transient bacteremia is also possible with daily practice (e.g., tooth brushing (40%) and gum chewing (20%)) and not only dental

treatments (e.g., extractions (35-80%) or periodontal surgery (30-88%); endocarditis is not only caused by bacteria; causative bacteria are resistant to the antibiotics administered as prophylaxis (i.e., amoxicillin); and the majority of bacterial endocarditis cases are independent of invasive procedures where only a minority are correlated with dental care. In a survey conducted by Tomas-Carmona et al. in Spain, it was found that fewer than 30% of observed dental professionals were aware of correct antibiotic indications and posology. On the other hand, prophylactic antibiotic administration for patients with total joint prostheses prior to invasive dental treatment does not hold much waters (54). In a study released by Jacobson et al. where only one out of 30 patients with infected prothesis there was a history of prior dental treatment.

Prophylaxis of local infection and systemic spread

It includes the administration of antibiotics before, during, or after the dental procedure to limit bacterial dissemination from the surgical wound. While some authors support such practice where it has shown to ameliorate the frequency of infectious complications following surgical extractions of lower third molars among patients receiving prophylaxis, others have reported no differences in the frequency of infections (2.09%) following periodontal surgery between patients receiving antibiotics perioperatively and those who were not (55). In a consensus agreement released by Gutierrez et al. (56) in 2006 on the use of antibiotic prophylaxis in dental surgery, antibiotics prophylaxis for healthy patients was only suggested following the removal of impacted teeth, periapical surgery, bone surgery, implant surgery, bone grafting and surgery for benign tumors. Immunocompromised patients (i.e., cancer patients, immune-suppressed individuals, patients with uncontrolled metabolic disorders such as diabetes, and splenectomized

patients) were also encouraged to receive prophylactic antibiotic prior to any invasive surgery.

Effect of antibiotics administration on wound healing

There is no clear evidence on the effect of antibiotics on dental wound healing. In a study run by Ranta et al., it has been suggested that there is no significant difference in wound healing between patients taking penicillin and the control groups (57).

Precautions with antibiotics use

Pregnancy

The legal and ethical considerations make it impossible to implement clinical trials to assess the risks associated with antibiotic use during pregnancy. The United States Food and Drug Administration (FDA) has established a new labeling rule starting from 2016 called the Pregnancy and Lactation Labeling Rule (PLLR) which have replaced the four levels of drug risk during pregnancy: (A) no demonstrated risk; (B) no effects in animals though not tested in humans; (C) teratogenic effects recorded in animals without proof in humans; (D) teratogenic effects upon the fetus, yet can be used if benefits outweigh the risk; and (X) teratogenic effects that outweigh any possible benefit derived from the drug. Group A drugs comprise no antibiotics. Group B (caution with treatment) contains the following antibiotics: azithromycin, cephalosporins, erythromycin, metronidazole and penicillins with or without beta-lactamase inhibitors. Group C includes clarithromycin, fluorquinolones and sulfa drugs (including dapsone). Finally, group D contains aminoglycosides and tetracyclines (58).

Kidney failure

Many antibiotics are renally eliminated, thus warranting precaution in renally impaired patients through dose adjustment (i.e., dose reduction or increased interval between doses) (59).

Bacterial resistance

Bacterial resistances is a paradigm issue for both the patient and public health. In a study conducted by Kuriyama et al. (60), it was demonstrated that ß-lactamase producing bacteria are being increasingly cultivated from odontogenic infections in patients that have previously received beta-lactams. It is worth mentioning that a heightened number of resistant bacterial strains is usually isolated from patients receiving the drug for longer durations. Therefore, a rational use of antibiotics is essential in dental practice to ensure maximal efficacy while minimizing the risk for resistance. A growing number of resistant strains is being detected in the oral cavity–Porphyromona, Prevotella (61), Streptoccocus viridans, against the following drugs–macrolides, penicillin, and clindamycin (62,63). While there is a low risk of resistance (< 10%) towards amoxicillin and the amoxicillin-clavulanic acid among most of the identified germs, Bacteroides and Prevotella intermedia have shown a higher rate of resistance (25%). Amoxicillin has shown resistance in 30-80% of all strains of Prevotella and Porphyromona. The commonly used antibiotics in dental practice (e.g., erythromycin, metronidazole, or azithromycin) were demonstrated to be ineffective for over 30% of bacterial strains (39.1%, 50.5% and 33.2%, respectively). However, the oxazolidinones, Linezolid, has proven to be effective in 94.6% of the strains including multi-resistant gram positive germs and anaerobes. Similarly, excellent sensitivity results (up to 98% of all strains) were obtained with

fluorquinolones (i.e., moxifloxacin and levofloxacin). Less sensitivity results (70-75%) were observed with doxycycline, clindamycin and penicillin.

Drug interactions

Almost often, antibiotics are prescribed along with nonsteroidal anti-inflammatory drugs (NSAIDs) in dental practice. An increased risk for drug-drug interaction is available between both categories. While some antibiotics come in combination with NSAIDS (e.g., cephalosporins and ibuprofen, or tetracyclines with naproxen or diclofenac) to increase in the bioavailability of the antibiotic, other NSAIDs reduce antibiotic bioavailability (63,64).

Conclusion:

In conclusion, dentists should ensure antibiotics are prescribed only when clinical signs and symptoms of bacterial infection suggest systemic immune response such as fever or malaise along with swelling. Also use the most targeted narrow spectrum antibiotic for shortest duration possible for otherwise healthy patients and document the diagnosis, treatment steps, rationale for antibiotic use in the patient progress report.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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