

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 amoxicillin 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](#).

Comment [MA1]: His

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

Comment [MA2]: Kindly mention broad spectrum antibiotics are the initial treatment protocol without culture report. Once the culture report has been obtained, broad spectrum could be changed to more specific one.

Comment [MA3]: Please change the word ineffective to "not having extra benefits". In case of localized orofacial infections, debridement and drainage is sufficient. Antibiotics could be used but has no extra benefits in terms of resolving the infection.

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.

Comment [MA4]: Please support your claim with adequate literature references.

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).

Comment [MA5]: Please be specific to which class of microorganism. You could add the most common type of pathogens contributing to an oral infection.

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

Comment [MA6]: Please be specific to include complications that leads to immuno-compromised state.

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.

Comment [MA7]: Please mention the reason for usefulness of beta lactam antibiotics over the other class of drugs.

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).

Comment [MA8]: Please change it to over the counter drugs or not authorized by the practice.

Comment [MA9]: Please add MRSA and vancomycin as a choice of drug to treat MRSA cases

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).

Comment [MA10]: Please expand the term.

Comment [MA11]: Please be specific about the classes of bacteria prevalent in endodontic infection.

Comment [MA12]: Please be specific about the hepatic changes

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

Comment [MA13]: Please cite the source from which the particular data have been obtained

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

Comment [MA14]: Please add effectiveness above which classes of drugs

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 due 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

Comment [MA15]: Please write in scientific terminology

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 water (54). In a study released by Jacobson et al. where only one out of 30 patients with infected prosthesis 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, antibiotic 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).

Comment [MA17]: Please add the dosage requirement and safe period for the use of drugs during pregnancy

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).

Comment [MA18]: Please mention class of antibiotics that are safe and contraindicated to patients with renal complications

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 β -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), *Streptococcus viridans*, against the following drugs—macrolides, penicillin, and clindamycin (62,63).

Comment [MA19]: Please rephrase the sentence.

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

Comment [MA20]: Please mention about MRSA

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).

Comment [MA21]: Please mention about potentially serious and life-threatening interactions of the antibiotics erythromycin, clarithromycin and metronidazole, and of the antifungal agents ketoconazole and itraconazole, with a host of other drugs whose metabolism is impaired by these antimicrobial agents

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.

References:

1. Leffler DA, Lamont JT. *Clostridium difficile* Infection. Longo DL, editor. N Engl J Med [Internet]. 2015 Apr 16 [cited 2021 Sep 15];372(16):1539–48. Available from: <http://www.nejm.org/doi/10.1056/NEJMra1403772>
2. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* Infection in the United States. N Engl J Med [Internet]. 2015 Feb 26 [cited 2021 Sep 15];372(9):825–34. Available from: <http://www.nejm.org/doi/10.1056/NEJMoa1408913>
3. Ventola C. The antibiotic resistance crisis: part 1: causes and threats. P & T: A peer reviewed journal for formulary management. 2015;40(4):277–83.
4. Cope A, Francis N, Wood F, Mann MK, Chestnutt IG. Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults. Cochrane Oral Health Group, editor. Cochrane Database Syst Rev [Internet]. 2014 Jun 26 [cited 2021 Sep 27]; Available from: <https://doi.wiley.com/10.1002/14651858.CD010136.pub2>

5. Fouad AF, Rivera EM, Walton RE. Penicillin as a supplement in resolving the localized acute apical abscess. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* [Internet]. 1996 May [cited 2021 Sep 27];81(5):590–5. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1079210496800540>
6. Henry M, Reader A, Beck M. Effect of Penicillin on Postoperative Endodontic Pain and Swelling in Symptomatic Necrotic Teeth. *J Endod* [Internet]. 2001 Feb [cited 2021 Sep 27];27(2):117–23. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0099239905607157>
7. Matthews DC, Sutherland S, Basrani B. Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. *J Can Dent Assoc*. 2003 Nov;69(10):660.
8. Walton RE, Chiappinelli J. Prophylactic penicillin: Effect on posttreatment symptoms following root canal treatment of asymptomatic periapical pathosis. *J Endod* [Internet]. 1993 Sep [cited 2021 Sep 27];19(9):466–70. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0099239906805352>
9. Nagle D, Reader A, Beck M, Weaver J. Effect of systemic penicillin on pain in untreated irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* [Internet]. 2000 Nov [cited 2021 Sep 27];90(5):636–40. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1079210400544333>
10. Pickenpaugh L, Reader A, Beck M, Meyers W, Peterson L. Effect of Prophylactic Amoxicillin on Endodontic Flare-Up in Asymptomatic, Necrotic Teeth. *J Endod* [Internet]. 2001 Jan [cited 2021 Sep 27];27(1):53–6. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0099239905600192>
11. Abbott AA, Koren LZ, Morse DR, Sinai IH, Doo RS, Lawrence Furst M. A prospective randomized trial on efficacy of antibiotic prophylaxis in asymptomatic teeth with pulpal necrosis and associated periapical pathosis. *Oral Surg Oral Med Oral Pathol* [Internet]. 1988 Dec [cited 2021 Sep 27];66(6):722–33. Available from: <https://linkinghub.elsevier.com/retrieve/pii/0030422088903246>
12. Fouad AF. Are antibiotics effective for endodontic pain? *Endod Top* [Internet]. 2002 Nov [cited 2021 Sep 27];3(1):52–66. Available from: <http://doi.wiley.com/10.1034/j.1601-1546.2002.30106.x>
13. Morse DR, Furst ML, Belott RM, Lefkowitz RD, Spritzer IB, Sideman BH. Infectious flare-ups and serious sequelae following endodontic treatment: A prospective randomized trial on efficacy of antibiotic prophylaxis in cases of asymptomatic pulpal-periapical lesions. *Oral Surg Oral Med Oral Pathol* [Internet]. 1987 Jul [cited 2021 Sep 27];64(1):96–109. Available from: <https://linkinghub.elsevier.com/retrieve/pii/003042208790123X>

14. Segura-Egea JJ, Velasco-Ortega E, Torres-Lagares D, Velasco-Ponferrada MC, Monsalve-Guil L, Llamas-Carreras JM. Pattern of antibiotic prescription in the management of endodontic infections amongst Spanish oral surgeons. *Int Endod J* [Internet]. 2010 Apr [cited 2021 Sep 27];43(4):342–50. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2591.2010.01691.x>
15. Yingling N, Ellenbyrne B, Hartwell G. Antibiotic Use by Members of the American Association of Endodontists in the Year 2000: Report of a National Survey. *J Endod* [Internet]. 2002 May [cited 2021 Sep 27];28(5):396–404. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S009923990560502X>
16. Tilburt JC, Emanuel EJ, Kaptchuk TJ, Curlin FA, Miller FG. Prescribing “placebo treatments”: results of national survey of US internists and rheumatologists. *BMJ* [Internet]. 2008 Oct 23 [cited 2021 Sep 27];337(oct23 2):a1938–a1938. Available from: <https://www.bmj.com/lookup/doi/10.1136/bmj.a1938>
17. König C. Bacterial concentrations in pus and infected peritoneal fluid--implications for bactericidal activity of antibiotics. *J Antimicrob Chemother* [Internet]. 1998 Aug 1 [cited 2021 Oct 2];42(2):227–32. Available from: <https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/42.2.227>
18. Aminoshariae A, Kulild JC. Evidence-based recommendations for antibiotic usage to treat endodontic infections and pain. *J Am Dent Assoc* [Internet]. 2016 Mar [cited 2021 Oct 2];147(3):186–91. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002817715010971>
19. Bascones Martínez A, Aguirre Urizar JM, Bermejo Fenoll A, Blanco Carrión A, Gay-Escoda C, González Moles MA, Gutiérrez Pérez JL, Jiménez Soriano Y, Liébana Ureña J, López-Marcos JF, Maestre Vera JR, Perea Pérez EJ, Prieto Prieto J, Vicente Rodríguez JC. Documento de consenso sobre el tratamiento antimicrobiano de las infecciones bacterianas odontogénicas. *Av. Odontostomatol* 2005; 21-6:311-331.
20. Rodríguez-Núñez A, Cisneros-Cabello R, Velasco-Ortega E, Llamas-Carreras JM, Torres-Lagares D, Segura-Egea JJ. Antibiotic Use by Members of the Spanish Endodontic Society. *J Endod* [Internet]. 2009 Sep [cited 2021 Oct 2];35(9):1198–203. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0099239909005111>
21. Segura-Egea JJ, Gould K, Şen BH, Jonasson P, Cotti E, Mazzoni A, et al. Antibiotics in Endodontics: a review. *Int Endod J* [Internet]. 2017 Dec [cited 2021 Oct 2];50(12):1169–84. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/iej.12741>
22. Mainjot A, D’Hoore W, Vanheusden A, Van Nieuwenhuysen J-P. Antibiotic prescribing in dental practice in Belgium: Antibiotic prescribing. *Int Endod J* [Internet]. 2009 Dec [cited 2021 Oct 2];42(12):1112–7. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2591.2009.01642.x>

23. Baumgartner J, Xia T. Antibiotic Susceptibility of Bacteria Associated with Endodontic Abscesses. *J Endod* [Internet]. 2003 Jan [cited 2021 Oct 3];29(1):44–7. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0099239905607947>
24. Jungermann GB, Burns K, Nandakumar R, Tolba M, Venezia RA, Fouad AF. Antibiotic Resistance in Primary and Persistent Endodontic Infections. *J Endod* [Internet]. 2011 Oct [cited 2021 Oct 3];37(10):1337–44. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0099239911008132>
25. Poeschl PW, Crepaz V, Russmueller G, Seemann R, Hirschl AM, Ewers R. Endodontic Pathogens Causing Deep Neck Space Infections: Clinical Impact of Different Sampling Techniques and Antibiotic Susceptibility. *J Endod* [Internet]. 2011 Sep [cited 2021 Oct 3];37(9):1201–5. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0099239911006601>
26. Montagner F, Castilho Jacinto R, Correa Signoretti FG, Scheffer de Mattos V, Grecca FS, Figueiredo de Almeida Gomes BP. Beta-lactamic Resistance Profiles in *Porphyromonas*, *Prevotella*, and *Parvimonas* Species Isolated from Acute Endodontic Infections. *J Endod* [Internet]. 2014 Mar [cited 2021 Oct 4];40(3):339–44. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0099239913009837>
27. Kapoor G, Saigal S, Elongavan A. Action and resistance mechanisms of antibiotics: A guide for clinicians. *J Anaesthesiol Clin Pharmacol* [Internet]. 2017 [cited 2021 Oct 3];33(3):300. Available from: <http://www.joacp.org/text.asp?2017/33/3/300/214313>
28. Pinheiro ET, Gomes BPF, Ferraz CCR, Teixeira FB, Zaia AA, Souza Filho FJ. Evaluation of root canal microorganisms isolated from teeth with endodontic failure and their antimicrobial susceptibility: *Microbiological evaluation of canals from root-filled teeth*. *Oral Microbiol Immunol* [Internet]. 2003 Apr [cited 2021 Oct 3];18(2):100–3. Available from: <http://doi.wiley.com/10.1034/j.1399-302X.2003.00058.x>
29. Khemalelakul S, Baumgartner JC, Pruksakorn S. Identification of bacteria in acute endodontic infections and their antimicrobial susceptibility. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* [Internet]. 2002 Dec [cited 2021 Oct 3];94(6):746–55. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1079210402003487>
30. Macy E. Penicillin and Beta-Lactam Allergy: Epidemiology and Diagnosis. *Curr Allergy Asthma Rep* [Internet]. 2014 Nov [cited 2021 Oct 3];14(11):476. Available from: <http://link.springer.com/10.1007/s11882-014-0476-y>
31. Albin S, Agarwal S. Prevalence and characteristics of reported penicillin allergy in an urban outpatient adult population. *Allergy Asthma Proc* [Internet]. 2014

- Nov 1 [cited 2021 Oct 3];35(6):489–94. Available from: <http://www.ingentaconnect.com/content/10.2500/aap.2014.35.3791>
32. Barr WH, Zola EM, Candler EL, Hwang S-M, Tendolkar AV, Shamburek R, et al. Differential absorption of amoxicillin from the human small and large intestine. *Clin Pharmacol Ther* [Internet]. 1994 Sep [cited 2021 Oct 3];56(3):279–85. Available from: <http://doi.wiley.com/10.1038/clpt.1994.138>
 33. Wright AJ. The Penicillins. *Mayo Clin Proc* [Internet]. 1999 Mar [cited 2021 Oct 3];74(3):290–307. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0025619611638676>
 34. Palmer N, Martin M. An investigation of antibiotic prescribing by general dental practitioners: a pilot study. *Prim Dent Care J Fac Gen Dent Pract UK*. 1998 Jan;5(1):11–4.
 35. Martin MV, Longman LP, Hill JB, Hardy P. Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. *Br Dent J* [Internet]. 1997 Aug [cited 2021 Oct 3];183(4):135–7. Available from: <http://www.nature.com/articles/4809444>
 36. Lewis MA, McGowan DA, MacFarlane TW. Short-course high-dosage amoxycillin in the treatment of acute dento-alveolar abscess. *Br Dent J* [Internet]. 1986 Oct [cited 2021 Oct 3];161(8):299–302. Available from: <http://www.nature.com/articles/4805959>
 37. Lacey RW, Howson G, Lord V, Luxton DEA, Trotter IS. DOUBLE-BLIND STUDY TO COMPARE THE SELECTION OF ANTIBIOTIC RESISTANCE BY AMOXYCILLIN OR CEPHRADINE IN THE COMMENSAL FLORA. *The Lancet* [Internet]. 1983 Sep [cited 2021 Oct 3];322(8349):529–32. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0140673683905664>
 38. Kim MK, Chuang S-K, August M. Antibiotic Resistance in Severe Orofacial Infections. *J Oral Maxillofac Surg* [Internet]. 2017 May [cited 2021 Oct 3];75(5):962–8. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0278239116310977>
 39. Nikaido H. Antibiotic Resistance Caused by Gram- Negative Multidrug Efflux Pumps. *Clin Infect Dis* [Internet]. 1998 Aug [cited 2021 Oct 3];27(s1):S32–41. Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1086/514920>
 40. Salvo F, Polimeni G, Moretti U, Conforti A, Leone R, Leoni O, et al. Adverse drug reactions related to amoxicillin alone and in association with clavulanic acid: data from spontaneous reporting in Italy. *J Antimicrob Chemother* [Internet]. 2007 Jul 1 [cited 2021 Oct 3];60(1):121–6. Available from: <http://academic.oup.com/jac/article/60/1/121/728466/Adverse-drug-reactions-related-to-amoxicillin>

41. Reusser F. Effect of Lincomycin and Clindamycin on Peptide Chain Initiation. *Antimicrob Agents Chemother* [Internet]. 1975 Jan [cited 2021 Oct 3];7(1):32–7. Available from: <https://journals.asm.org/doi/10.1128/AAC.7.1.32>
42. Skucaite N, Peciuliene V, Vitkauskiene A, Machiulskiene V. Susceptibility of Endodontic Pathogens to Antibiotics in Patients with Symptomatic Apical Periodontitis. *J Endod* [Internet]. 2010 Oct [cited 2021 Oct 3];36(10):1611–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S009923991000381X>
43. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-Analysis of Antibiotics and the Risk of Community-Associated *Clostridium difficile* Infection. *Antimicrob Agents Chemother* [Internet]. 2013 May [cited 2021 Oct 4];57(5):2326–32. Available from: <https://journals.asm.org/doi/10.1128/AAC.02176-12>
44. Buffie CG, Jarchum I, Equinda M, Lipuma L, Gobourne A, Viale A, et al. Profound Alterations of Intestinal Microbiota following a Single Dose of Clindamycin Results in Sustained Susceptibility to *Clostridium difficile*-Induced Colitis. McCormick BA, editor. *Infect Immun* [Internet]. 2012 Jan [cited 2021 Oct 4];80(1):62–73. Available from: <https://journals.asm.org/doi/10.1128/IAI.05496-11>
45. Cachovan G, Böger RH, Giersdorf I, Hallier O, Streichert T, Haddad M, et al. Comparative Efficacy and Safety of Moxifloxacin and Clindamycin in the Treatment of Odontogenic Abscesses and Inflammatory Infiltrates: a Phase II, Double-Blind, Randomized Trial. *Antimicrob Agents Chemother* [Internet]. 2011 Mar [cited 2021 Oct 4];55(3):1142–7. Available from: <https://journals.asm.org/doi/10.1128/AAC.01267-10>
46. Adriaenssen C. Comparison of the Efficacy, Safety and Tolerability of Azithromycin and Co-Amoxiclav in the Treatment of Acute Periapical Abscesses. *J Int Med Res* [Internet]. 1998 Oct [cited 2021 Oct 4];26(5):257–65. Available from: <http://journals.sagepub.com/doi/10.1177/030006059802600506>
47. Isla A, Canut A, Rodriguez Gascon A, Pedraz JL. Farmacocinética/framacodinámica de la formulacion de amoxicilina/acido clavulanico 1000/62,5 mg en odontoestomatologia. *Enferm Infecc Microbiol Clin* 2005;23:387.
48. Poeschl PW, Spusta L, Russmueller G, Seemann R, Hirschl A, Poeschl E, et al. Antibiotic susceptibility and resistance of the odontogenic microbiological spectrum and its clinical impact on severe deep space head and neck infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* [Internet]. 2010 Aug [cited 2021 Oct 4];110(2):151–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1079210409009809>
49. Bystedt H, Dahlbäck A, Dornbusch K, Nord CE. Concentrations of azidocillin, erythromycin, doxycycline and clindamycin in human mandibular bone. *Int J Oral*

- Surg [Internet]. 1978 Oct [cited 2021 Oct 4];7(5):442–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0300978578800350>
50. Lindeboom JAH, Frenken JWH, Valkenburg P, van den Akker HP. The role of preoperative prophylactic antibiotic administration in periapical endodontic surgery: a randomized, prospective double-blind placebo-controlled study. *Int Endod J* [Internet]. 2005 Dec [cited 2021 Oct 4];38(12):877–81. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2591.2005.01030.x>
 51. Moreno-Drada JA, García-Perdomo HA. Effectiveness of Antimicrobial Prophylaxis in Preventing the Spread of Infection as a Result of Oral Procedures: A Systematic Review and Meta-Analysis. *J Oral Maxillofac Surg* [Internet]. 2016 Jul [cited 2021 Oct 4];74(7):1313–21. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0278239116003402>
 52. Marcussen KB, Laulund AS, Jørgensen HL, Pinholt EM. A Systematic Review on Effect of Single-Dose Preoperative Antibiotics at Surgical Osteotomy Extraction of Lower Third Molars. *J Oral Maxillofac Surg* [Internet]. 2016 Apr [cited 2021 Oct 4];74(4):693–703. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0278239115015542>
 53. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al. PREVENTION OF BACTERIAL ENDOCARDITIS: RECOMMENDATIONS BY THE AMERICAN HEART ASSOCIATION. *J Am Dent Assoc* [Internet]. 1997 Aug [cited 2021 Oct 4];128(8):1142–51. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0002817715604330>
 54. Pallasch TJ, Slots J. Antibiotic prophylaxis and the medically compromised patient. *Periodontol 2000* [Internet]. 1996 Feb [cited 2021 Oct 4];10(1):107–38. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/j.1600-0757.1996.tb00071.x>
 55. Powell CA, Mealey BL, Deas DE, McDonnell HT, Moritz AJ. Post-Surgical Infections: Prevalence Associated With Various Periodontal Surgical Procedures. *J Periodontol* [Internet]. 2005 Mar [cited 2021 Oct 4];76(3):329–33. Available from: <http://doi.wiley.com/10.1902/jop.2005.76.3.329>
 56. Gutiérrez JL, Bagán JV, Bascones A, Llamas R, Llena J, Araceli Morales, Noguerol B, Planells P, Prieto J, Salmerón JI. Documento de consenso sobre la utilización de profilaxis antibiótica en cirugía y procedimientos dentales. *Av. Odontoestomatol* 2006; 22-1: 41-67.
 57. Ranta H, Haapasalo M, Ranta K, Kontiainen S, Kerosuo E, Valtonen V, et al. Bacteriology of Odontogenic Apical Periodontitis and Effect of Penicillin Treatment. *Scand J Infect Dis* [Internet]. 1988 Jan [cited 2021 Oct 4];20(2):187–92. Available from: <http://www.tandfonline.com/doi/full/10.3109/00365548809032436>

58. Michavila A, Flórez J, García-Lobo JM. Farmacología de las enfermedades infecciosas. Principios generales, selección y asociación de antibióticos. En: Flórez J. Ed. Farmacología humana 4aed. Barcelona: Masson SA; 2005. p. 1081-103
59. Livornese LL, Slavin D, Gilbert B, Robbins P, Santoro J. Use of antibacterial agents in renal failure. *Infect Dis Clin North Am* [Internet]. 2004 Sep [cited 2021 Oct 4];18(3):551–79. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0891552004000765>
60. Kuriyama T, Nakagawa K, Karasawa T, Saiki Y, Yamamoto E, Nakamura S. Past administration of β -lactam antibiotics and increase in the emergence of β -lactamase-producing bacteria in patients with orofacial odontogenic infections. *Oral Surg Oral Med Oral Pathol Oral Radiol Endodontology* [Internet]. 2000 Feb [cited 2021 Oct 4];89(2):186–92. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1079210400067421>
61. Bresco-Salinas M, Costa-Riu N, Berini-Aytes L, Gay-Escoda C. Susceptibilidad antibiótica de las bacterias causantes de infecciones odontogénicas. *Med Oral Patol Oral Cir Bucal* 2006;11:51-6.
62. Aracil B. High prevalence of erythromycin-resistant and clindamycin-susceptible (M phenotype) viridans group streptococci from pharyngeal samples: a reservoir of *mef* genes in commensal bacteria. *J Antimicrob Chemother* [Internet]. 2001 Oct 1 [cited 2021 Oct 4];48(4):592–4. Available from: <https://academic.oup.com/jac/article-lookup/doi/10.1093/jac/48.4.592>
63. Groppo FC, Castro FM, Pacheco AB, Motta RH, Filho TR de M, Ramacciato JC, et al. Antimicrobial resistance of *Staphylococcus aureus* and oral streptococci strains from high-risk endocarditis patients. *Gen Dent*. 2005 Dec;53(6):410–3.
64. Groppo FC, Simões RP, Ramacciato JC, Rehder V, Andrade ED de, Mattos-Filho TR. Effect of Sodium Diclofenac on Serum and Tissue Concentration of Amoxicillin and on Staphylococcal Infection. *Biol Pharm Bull* [Internet]. 2004 [cited 2021 Oct 4];27(1):52–5. Available from: http://www.jstage.jst.go.jp/article/bpb/27/1/27_1_52/_article
65. Decassiabergamaschi C, Motta R, Franco G, Cogo K, Montan M, Ambrosano G, et al. Effect of sodium diclofenac on the bioavailability of amoxicillin. *Int J Antimicrob Agents* [Internet]. 2006 May [cited 2021 Oct 4];27(5):417–22. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0924857906000501>