



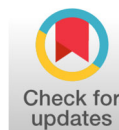
International Journal of Clinical and Medical Research

Received: September 27, 2024 | Accepted: November 11, 2024 | Published: December 30, 2024
Volume 01, Issue 02, Pages 23-31

DOI <https://doi.org/10.66590/ijcmr2024010203>

Review Article

OPEN ACCESS



Antibiotics and Analgesics in Endodontic Practice: A Comprehensive Review

Abdulilah A Albedair^{1*}

¹College of Medicine, University of Hail, Hail, Saudi Arabia

Author Designation: ¹Researcher

*Corresponding author: Abdulilah A Albedair (e-mail: Dr.Abdulilah.Albedair@gmail.com).

How to Cite the Article:

A Albedair, Abdulilah. "Antibiotics and Analgesics in Endodontic Practice: A Comprehensive Review." *International Journal of Clinical and Medical Research*, vol. 01, no. 02, December 2024, pp. 23-31. <https://doi.org/10.66590/ijcmr2024010203>

Abstract | Bacteria are the primary causative agents in the development and progression of pulpal and periapical diseases. The main objective of endodontic treatment is to eliminate as many microorganisms as possible from the root canal system and to create conditions that prevent the survival and proliferation of any remaining bacteria. This goal can be achieved through a combination of local and systemic antimicrobial therapy. During endodontic treatment, antibiotics may be administered systemically or locally to help establish and maintain an aseptic environment. This review discusses the role, indications, and applications of antibiotics in endodontic practice.

Key Words: Antibiotics, Antibiotic Prophylaxis, Endodontics, Immuno-Compromised, Systemic Use

INTRODUCTION

More than 700 species of microorganisms belonging to 11 different divisions have been identified within the oral cavity. Endodontic infections primarily involve the root canal system, where microorganisms play a significant role in the initiation and progression of pulpal and periapical diseases. The bacteria associated with primary endodontic infections are usually polymicrobial, predominantly consisting of Gram-negative anaerobic rods, whereas secondary infections are commonly associated with one or a few bacterial species, most notably *Enterococcus faecalis* [1].

The primary objective of endodontic treatment is to eliminate as many microorganisms and their toxic by-products as possible from the root canal system through the use of various antimicrobial strategies, thereby creating an environment unfavorable for microbial survival [2]. The discovery of penicillin by Alexander Fleming in 1928 revolutionized healthcare, including both medicine and dentistry [3]. In endodontic practice, antibiotics may be administered either systemically or locally. Systemic antibiotics should only be prescribed for dental infections when clearly indicated [4]. However, because systemic antibiotics often fail to adequately

penetrate necrotic pulp tissue, the local application of antibiotics has become an effective approach for root canal disinfection [5].

History

Mixtures with antimicrobial properties utilized in the treatment of infections were described over 2,000 years ago [6]. Traditionally, plant materials and extracts [7], honey [8], moldy soybean curd, warm earth rich in moulds and fungi were used to treat infections. These folk remedies tell the tale of inadvertent use of antibiotics since ages, although the concept of antibiotics is relatively recent.

Physician Paul Ehrlich laid down the foundation of idea of antibiotics by introducing the term "magic bullets" for a chemical that would attach itself to the germ and kill it. Jean Paul Vuillemin used the term "antibiosis" that means "against life" for early antibacterial drugs [9]. Antibiosis was first described in 1877 by Louis Pasteur and Robert Koch [10]. In 1942, Selman Waksman referred antibacterial drugs as antibiotics to describe any substance produced by a micro-organism that is antagonistic to the growth of other micro-organisms in a high dilution [11]. Grossman, known as father of endodontics

Table 1: Studies on Antibiotic Prescribing by Dentists in European Countries

Authors	Country	Prescriber	First Prescribed Antibiotic	Second Prescribed Antibiotic	Antibiotic in Allergic Patient	Duration (days)
Palmer <i>et al.</i>	UK	General Practitioner	Amoxicillin	Penicillin VK	Metronidazole	5 (3-10)
Kandemir and Ergul	Turkey	General Practitioner	Ampicillin	Amoxicillin	—	—
Dailey and Martin	UK	General Practitioner	Amoxicillin	Amoxicillin / Metronidazole	—	—
Tulip and Palmer	UK	General Practitioner	Amoxicillin	Metronidazole	—	—
Rodriguez-Nuñez <i>et al.</i>	Spain	Endodontist	Amoxicillin	Metronidazole / Spiramycin	Clindamycin	6.8±1.8
Mainjot <i>et al.</i>	Belgium	General Practitioner	Amoxicillin	Clindamycin	Erythromycin	—
Skucaite <i>et al.</i>	Lithuania	General Practitioner	Amoxicillin	Penicillin VK	—	—
Segura-Egea <i>et al.</i>	Spain	Dental Surgeon	Amoxicillin	Clindamycin	Clindamycin	7.0±1.0
Kaptan <i>et al.</i>	Turkey	General Practitioner	Amoxicillin	Clindamycin	Clindamycin	—
Peric <i>et al.</i>	Croatia	Dental Surgeon	Amoxicillin	Clindamycin	Clindamycin	6.4±1.6

in 1951 proposed PBSC (polyantibiotic paste which suspended in a silicone vehicle, and was a combination of penicillin, bacitracin, streptomycin and caprylate sodium), that was the firstly reported local use of an antibiotic in endodontics [12]. Polyantibiotic paste showed therapeutic potential, but owing to the drawbacks including ineffectiveness against anaerobic species and allergic reactions, the Food and Drug Administration (FDA) prohibited PBSC for endodontic use in 1975. Later, an antifungal version of PBSC named with PBSN, in which Nystatin substituted caprylate sodium, was released [13]. In Europe, several surveys have studied the pattern of antibiotic prescribing in the treatment of endodontic diseases (Table 1).

Antibiotics

These are available either singly or in combination of antibiotics, and may also sometimes incorporate some other compounds such as corticosteroids. Antibiotics can be used systemically or locally as an adjunct to endodontic treatment [14]. Grossman records the first reported case in the literature, to use antibiotics locally in the endodontic treatment which was known as PBSC which contained penicillin to target Gram-positive organisms, bacitracin for penicillin-resistant strains, streptomycin for Gram-negative organisms, and caprylate sodium to target yeasts with all these compounds suspended in a silicone vehicle. Ledermix™ paste and Septomixine Forte™ paste are the two most common antibiotic-containing commercial paste preparations which are currently available. Both of these commercial formulations also contain corticosteroids as anti-inflammatory agents [15].

One of the common protocols used these days is the Antibiotic prophylaxis (AP) which involves use of antimicrobial agent before commencement of any infection, for the purpose of preventing a subsequent infection [16,17]. Infective Endocarditis (IE) requires lots of serious attention because of its high morbidity and mortality rate. Therefore, it is necessary and advised that AP is required before dental procedures which are likely to induce bacteraemia. But data quotes low incidence of IE and also there is no evidence that AP is either effective or ineffective against IE in people undergoing or about to undergo various dental procedures [18].

Literature quotes studies that show IE during dental Procedures includes various protocols, theories and methods generally utilized to support relation and association between various invasive dental procedures, bacteraemia and occurrence of subsequent infective endocarditis includes:

- Animal experimentation
- Providing sure evidence that AP preoperatively is protective against infective endocarditis with the inference that the procedure was the cause of the disease in the unprotected
- To have sure evidence that dental procedures actually produces bacteraemia

Antibiotic Prophylaxis

The protocol proposed by the American Heart Association states that antibiotics must be administered one hour (oral route) or 30 minutes (intravenous route) before the procedure.

The principles of antibiotic prophylaxis include the following:

- Satisfactory risk and cost-benefit ratios should exist in which benefit to the patient
- Significantly outweighs medical and financial risks
- The antibiotic must be in high concentrations at the target site
- An antibiotic loading dose (2 to 4 times the maintenance dose) must be used
- The antibiotic is continued only as long as microbial contamination from an operative site continues

Conditions Requiring

- Previous history of endocarditis.
- Total joint replacement.
- Complex and cyanotic congenital heart diseases.
- Surgically constructed pulmonary shunts.
- Rheumatic heart diseases.
- Mitral valve prolapses
- Valvular regurgitation
- Prosthetic valve replacement.

- Uncontrolled diabetes mellitus [19]

Two mechanisms are mainly involved for providing AP before dental procedures which are likely to produce a bacteraemia because of IE. First one involves reduction in the number of organisms in the blood and the second one includes reduction in the adhesion of organisms to the nonbacterial thrombotic vegetation [20].

Various different methods have been brought up for reducing bacteraemia, apart from conventional method of antibiotic prophylaxis of IE. This includes use of pre-operative 1% povidone iodine for reducing bacteraemia from oral sources [21,22]. In one of the double-blind trial including 60 patients involved in taking pre-extraction rinsing with 1% (v/v) chlorhexidine, 1% (v/v) povidoneiodine and a control of NaCl, showed a significant reduction in bacteraemia between both antimicrobials and the control was shown [23].

From current knowledge and based on the International Association of Dental Traumatology (IADT) guidelines, the following recommendations can be made in terms of antibiotic administration following traumatic dental injuries.

Pain Control

Pain controlling or analgesic medications are broadly categorized in three categories. Narcotics being the most powerful one and have three types of receptors in the brain. Second category includes Aspirin and the NSAIDs which mainly act at the site of injury causing reduction in pain-invoking prostaglandins that are made within the damaged cell. Narcotics have side-effect of causing addiction, with characteristics unique from other types of addiction. This addiction includes both physical and psychological one. They form on the main line of treatment in patients reporting with history of drug allergies. The practitioners are left with no choice except for prescribing narcotics.

Propoxyphene was originally introduced as a non-narcotic; however, with time and researches, it is now known to be rather a weak narcotic. In spite of its weak line of action, it is still effective in many patients may be because of its certain characteristic features including dizziness which makes the patient feel that it must be helping with the pain. Darvon® is available in single plain formulation or in combination with aspirin or with acetaminophen, called as Darvocet-N®.

Oramorph® is the oral formulation of morphine. Oral drugs have usually rapid liver metabolism, therefore, mostly a larger dose is required than is typical of the parenteral dose. NSAIDs (Motrin/Advil) usually do not cause interruption of platelet synthesis for nearly as long because their binding to cyclo-oxygenase is reversible. Shortly after the NSAIDs are metabolized, bleeding profiles return to normal. Acetaminophen (Tylenol) gives patients relief but the mode of action and the site of action

in brain is unknown. Other formulation containing aspirin and acetaminophen includes Excedrin®, Goody's Headache Powder®. Patients with chronic liver disease, alcohol users or with liver abnormalities should use Acetaminophen is with great caution as it is metabolized by the liver. Recent study research data shows that acetaminophen is a better choice for the elevation of the threshold for sharp pain, such as with dental treatment, than other types of pain relievers [24,25].

Types of Antibiotics and Recommended Dosages in Endodontics

Amoxicillin is a moderate-spectrum, bacteriolytic, beta-lactam antibiotic that represents a synthetic improvement upon the original penicillin molecule. It is a good drug for orofacial infections because it is readily absorbed (better than penicillin) and can be taken with food. It is better able to resist damage from stomach acid so less of an oral dose is wasted; it also has a much broader spectrum against the gram-negative cell wall than penicillin, and appropriate blood levels are retained for a slightly longer time [26]. However, amoxicillin is susceptible to degradation by beta-lactamase producing bacteria, and often is given with clavulanic acid to increase its spectrum against *Staphylococcus aureus*.

Co-amoxiclav (amoxicillin/ clavulanic acid) is one of the antibiotics recommended for the treatment of odontogenic infections due to its sufficiently wide spectrum, greater antibacterial effectiveness than penicillin VK, low incidence of resistance, pharmacokinetic profile, tolerance and dosage [27,28] and low resistance of bacteria cultivated from root canal samples [29]. However, evidence-based guidelines recommend that due to its greater potential for the emergence of antibiotic-resistant bacterial strains and association with increased risk of *Clostridium difficile* infection, it should be reserved for immune-compromised patients or those infections that have not responded to first-line antimicrobial therapy when provided in conjunction with operative treatment [30]. Due to its longer half-life and more sustained serum levels, amoxicillin is taken three times a day and costs only slightly more than penicillin.

The recommended oral dosage of amoxicillin with or without clavulanic acid is 1000 mg loading dose followed by 500 mg every 8 h (Table 2). It has been argued that amoxicillin has a broader spectrum than is required for endodontic needs and, therefore, its use in a healthy individual could contribute to the global problem of antibiotic resistance [31]. However, this argument is old and not justified. There is no doubt that the use of antibiotics in general should be restricted to those cases where there is a clear indication for them; however, whether the selection of one type over another with a slightly wider spectrum can contribute to the global resistance problem is not well reasoned. Even more

Table 2: Effective Antibiotics Prescribed in Endodontics (References in the Text)

Drug of choice	Loading dose	Maintenance dose
Penicillin VK ^a	1000 mg	500 mg q4–6 h
Amoxicillin with or w/o Clavulanic acid	1000mg	500 mg q8 h or 875 mg q12 h
Clindamycin ^b	600 mg	300 mg q6 h
Clarithromycin ^b	500 mg	250 mg q12 h
Azithromycin ^b	500 mg	250 mg q24 h
Metronidazole	1000 mg	500 mg q6 h

important than slightly better antimicrobial spectrum, amoxicillin is better absorbed, and can therefore be used in a lower dose and may thus, reduce the gastrointestinal side effects. On the other hand, penicillin-induced diarrhoea may even further reduce antibiotic absorption, decreasing antibiotic levels in circulation and in the infected area.

^aIf Penicillin VK alone is not effective in 48–72 h, metronidazole (loading dose 1000 mg followed by 500 mg q6 h) can be used in combination with penicillin VK or penicillin VK is switched to amoxicillin/clavulanic acid or clindamycin. ^bIf the patient is allergic to penicillin.

Penicillin V is a narrow-spectrum antibiotic for infections caused by aerobic gram-negative cocci, facultative and anaerobic microorganism [32]. It has selective toxicity and exerts its antibacterial effect by the inhibition of cell wall production in bacteria. However, penicillin is not well absorbed from the intestinal tract, meaning that at least 70% of an oral dose is wasted, with diarrhoea as a frequent side effect. Penicillin is also a short-acting medication, with half of the amount circulating being removed from the body every half hour [32].

It has been documented that the majority of microorganisms have susceptibility to penicillin; therefore, it can be a good first option for the adjunctive treatment for lesions of endodontic origin. However, amoxicillin has a wide spectrum against endodontic pathogens. Testing antibiotic susceptibility on a panel of bacteria isolated from endodontic infections, the percentages of susceptibility for the 98 species analysed were 85% for penicillin V, 91% for amoxicillin, 100% for amoxicillin/clavulanic acid, 96% for clindamycin and 45% for metronidazole [33].

In a clinical study with 94 patients with abscesses, 98% were polymicrobial. Penicillin successfully treated the pathogens derived from odontogenic abscess sufficiently, when adequate surgical treatment was provided. Patients with good general health, small abscesses and without systemic symptoms were treated successfully with incision and drainage only. However, this study took place in a hospital and the standard regimen for adult patients was 5 million units penicillin G intravenously every 8 h for 5 days. Taking into account that IV penicillin G does not suffer from poor absorbance, this may have affected the outcome of the study [34].

A loading dose of 1000 mg of penicillin V should be administered orally followed by 500 mg every 4–6 h to

achieve a steady serum level [35]. Following debridement of the root canal system and drainage, significant improvement should be seen within 48–72hr. However, if penicillin V therapy is ineffective, another antibiotic should be selected, ideally following culture and sensitivity testing. Clindamycin is a good alternative [36]. In case no response occurs, consultation with a specialist will be necessary.

Although penicillin is generally the antibiotic of choice in infections of endodontic origin, one disadvantage associated with its use is the possibility of allergic reactions. Approximately 8% of the population have a history of penicillin allergy, but less than one in 20 have been confirmed clinically using the gold standard test for IgE-mediated penicillin allergy [37]. Unverified penicillin allergy is being increasingly recognized as a significant public health problem [38,39]. In patients with a confirmed penicillin allergy history, the clinician can switch to other antimicrobial agents such as clindamycin, metronidazole and clarithromycin or azithromycin [40,41]. However, dentists must not overuse non-beta-lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation. As a minimum, the clinician should ask about the symptoms of allergy from the patient. It must be remembered that some patients may report intolerance symptoms like diarrhoea or upset stomach, as an allergy.

Clindamycin belongs to the lincosamide class of antibiotics. It kills microorganisms by blocking their ribosomes. It is effective against most gram-positive aerobes and both gram-positive and gram-negative facultative bacteria and anaerobes. The distribution of this antibiotic in most body tissues is effective and has a bone concentration approximating to that in the plasma [40]. The adult oral dosage is 600 mg loading dose followed by 300 mg every 6 h [42].

Metronidazole is a nitroimidazole that is used either as an antiprotozoal agent or an antibiotic against anaerobic bacteria, and has been suggested as a supplemental medication for amoxicillin because of its excellent activity against anaerobes [31]. Because there are many bacteria resistant to metronidazole and it is not effective against aerobic and facultative bacteria, [33,36], it is generally used in combination with penicillin or clindamycin. Metronidazole used in combination with penicillin V or amoxicillin increased the susceptibility to 93% and 99% of bacteria, respectively [33]. The adult oral dosage is 1000 mg loading dose followed by 500 mg every 6 h.

Clarithromycin and azithromycin belong to the macrolide group of antibiotics. They are effective against a variety of aerobic and anaerobic gram-positive and gram-negative bacteria with improved pharmacokinetics [43]. Whilst the usual oral dosage for clarithromycin is a 500-mg loading dose followed by 250 mg every 12 h, the dosage for azithromycin is a loading dose of 500 mg followed by 250 mg once a day.

Duration of Antibiotic Therapy

The duration of antibiotic use in endodontic infections has not been defined precisely. Even though some dental practitioners consider that bacterial infections require 'a complete course' of antibiotic therapy [44], there is a general tendency to administer an antibiotic for 3–7 days [45] (Table 1). As prolonged antibiotic usage destroys the commensal flora in the oral cavity and other body sites and terminates colonization resistance [46], the use and duration of systemic antibiotic therapy must be reasonable. There is a common misconception that prolonged antibiotic administration is necessary even after clinical remission of the infection in order to avoid rebound infection.

Endodontic infections do not rebound when the source of periapical infection is properly eradicated, which is complete debridement, irrigation and disinfection of an infected root canal. Because these types of infections persist for several days, patients receiving antibiotics should be observed on a daily basis. The only guide for determining the effectiveness of antibiotic therapy and local endodontic intervention is the clinical improvement in the patient's symptoms. When there is ample clinical evidence that the symptoms are resolving or resolved, the antibiotic therapy should be ceased [31].

Fazakerley *et al.* and Martin *et al.* [45] (compared three antibiotics and duration of usage (2, 3 and 10 days). They reported that the majority of the patients were asymptomatic after 2 days. Despite the fact that antibiotics are very useful tools in cases posing risk for the patient, one should always bear in mind that they are not substitutes for endodontic treatment. The key to obtaining a successful result in an endodontic infection is the chemo-mechanical removal of the infecting agent from the root canal system as well as drainage of pus. The indications for antibiotic administration should be considered very carefully and only as an adjunct to endodontic treatment, which is the major and indispensable procedure for obtaining the optimum outcome in lesions of endodontic origin. When antibiotic usage is prescribed rationally and restricted to indicated cases only, favourable results are likely to be obtained for the complete eradication of the infection.

Antibiotic Prophylaxis for Medically Compromised Patients

The aim of antibiotic prophylaxis is to prevent local postoperative infections and prevent metastatic spread of

infection in susceptible individuals. Most individuals do not need antibiotic prophylaxis in connection with dental care. The microorganisms are scavenged from the bloodstream within minutes up to 1 h without causing any complications in healthy individuals.

Over the years, the clinical recommendations for antibiotic prophylaxis have changed and there is a trend towards a definite position [47,48]. The risk of adverse reactions to antibiotics and increasing development of drug-resistant bacteria outweigh the benefits of prophylaxis for most patients [49]. Antibiotics should only be given prophylactically in cases where the benefit has been demonstrated or where consensus exists as to such use [50].

Antibiotic prophylaxis may be considered for certain patient groups with impaired immunologic function. Surgical endodontic treatment on teeth with persistent infection after orthograde treatment is considered a higher medical burden than conventional endodontic treatment and patients at risk may benefit from antibiotic prophylaxis to a greater extent.

According to the literature, there are only a few risk conditions in which it is shown that antibiotic prophylaxis may be of benefit to the patient in conjunction with dental procedures [51]. However, there may be other patient groups in which antibiotic prophylaxis may be of benefit, but case-control studies or double-blinded studies within placebo have not been performed for ethical reasons.

Individuals who are immuno-compromised are less capable of battling infections because of an immune response that is not properly functioning. Causes of immunodeficiency can be acquired (such as leukaemia or HIV/AIDS), chronic disease (such as end-stage renal disease and dialysis or uncontrolled diabetes), medication (such as chemotherapy, radiation, steroids or immunosuppressive post-transplant medications) or genetic (such as inherited genetic defects). For most of these medical conditions, the treatment must be planned in close collaboration with physicians. For some medical conditions, the treatment must be preceded by a blood sample. Severity of neutropenia relates to the relative risk of infection and is categorized as mild ($1000\text{--}1500\ \mu\text{L}^{-1}$), moderate ($500\text{--}1000\ \mu\text{L}^{-1}$) and severe ($< 500\ \mu\text{L}^{-1}$). When neutrophil counts fall to $< 500\ \mu\text{L}^{-1}$, endogenous microbial flora (e.g. in the mouth or gut) can cause infections [52].

Patients with *Locus Minoris Resistentiae*

Locus minoris resistentiae refers to a body region more vulnerable than others, such as internal organs or external body regions with a congenital or acquired altered defence capacity [53]. Infective endocarditis, a bacterial infection of the heart valves or the endothelium of the heart, is a typical case of locus minoris resistentiae [54]. Individuals with certain pre-existing heart defects are considered at risk for developing endocarditis when a bacteraemia occurs [55]. Antibiotic prophylaxis has for a long time been considered as best practice for all patients

with complex congenital heart defects, prosthetic cardiac valve or a history of infective endocarditis [56].

According to the guidelines of the American Heart Association, individuals who are at risk of developing infective endocarditis following an invasive dental procedure still benefit from antibiotic prophylaxis, even if little evidence exists to support its effectiveness [57]. In contrast, the guidelines of the National Institute for Health and Clinical Excellence in the UK have recommended that prophylactic antibiotic treatment should no longer be prescribed for any at-risk patients [58]. Even though a recent retrospective follow-up study has indicated that the incidence of infective endocarditis has increased in the UK as the more restrictive recommendations were introduced [59], a causal relationship has not been shown between IE and dental procedures. Therefore, routine prescription of antibiotic prophylaxis before endodontic treatment of patients considered at risk for endocarditis may not be justified.

However, recently, NICE has made a significant change to Clinical Guideline 64 (CG64), 'Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures', adding the word 'routinely' to Recommendation 1.1.3, that now is as follows: Antibiotic prophylaxis against infective endocarditis is not recommended routinely for people undergoing dental procedures. The addition of the word 'routinely' makes it clear that in individual cases, antibiotic prophylaxis may be appropriate [60]. The guidelines of the European Society of Cardiology (ESC) for the management of infective endocarditis recommended antibiotic prophylaxis only for dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa, including scaling and root canal procedures [61].

The scientific evidence is insufficient to indicate providing antibiotic prophylaxis before dental treatment for healthy patients after prosthetic joint replacement [62,63], but this is still considered a dilemma for the clinician. This is partly on anecdotal grounds, partly historical and partly for legal concerns. A prospective case-control study concluded that dental procedures were not risk factors and the use of antibiotic prophylaxis prior to dental procedures did not decrease the risk of subsequent total hip or knee infection [64,65]. The joint guideline by American Academy of Orthopaedic Surgeons and American Dental Association in 2012 (http://www.aaos.org/uploaded_Files/PreProduction/Quality/Guidelines_and_Reviews/PUDP_guideline.pdf) states: 'The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures', but they also recognize that the evidence is limited, and the practitioner should exercise judgment in decision. In general, the risk is

considered to be elevated during the first 3 months after joint operations because endothelialization is not complete, and in case invasive dental treatments are necessary, antibiotic prophylaxis is recommended [66], as well as in patients with compromised host defence undergoing extensive dental procedures [67,68]. In patients with artificial joints, previous recent infection of the joint and cases with massive oral infections are considered high risk factors for prosthetic joint infections and antibiotic prophylaxis should be prescribed [64,65].

Jawbones exposed to high dose of radiation for cancer treatment in the head and neck results in lifelong changes in microcirculation and are thus more susceptible to local infection-related complications [69]. Dental treatment with a risk to translocate infection to the bone in high-dose exposed areas should be preceded by antibiotic prophylaxis [70].

Medication with bisphosphonates changes the bone turnover and prevents loss of bone mass. Several types of bisphosphonates have different indications and varying risks of developing osteonecrosis and changes in the bone that is then more prone to develop infections. The risk is substantially greater for patients receiving bisphosphonates for cancer than for osteoporosis. Other risk factors may include concomitant use of glucocorticoids, old age (over 65 years), poorly controlled diabetes, intravenous administration and prolonged use of bisphosphonates (more than 3 years). Invasive dental procedures of the alveolar bone modified by bisphosphonates, with subsequent infection in the bone, have been linked to the development of osteonecrosis [71].

Intravenous bisphosphonate treatment as an accompanying therapy for advanced tumour diseases warrants antibiotic prophylaxis in bone invasive procedures [72].

In all treatment situations, an overall medical assessment must be based on the individual case and consideration of the risk of infection-related complications as well as the risk of adverse drug reaction. Prophylaxis may sometimes not be justified according to the medical condition in connection with dental treatment, but can be justified when considering multiple medical conditions and age, or when several risk factors predispose patients to infections (such as poorly controlled or uncontrolled diabetes mellitus, malignancy, chronic inflammatory disease, immunosuppressive disease or treatment with immunosuppressive medication). In cases of doubt over the proper management of patients prior to dental treatment, the state and control of the disease of the patient should be discussed with a physician. The choice of drug should reflect its clinical efficacy, as well as whether it is safe and has a good spectrum. The suggested prophylaxis regimen [57].

CONCLUSIONS

The use of systemic antibiotics in endodontics should be limited to specific cases so as to avoid their over prescription. They can be used as an adjunct in the treatment of apical periodontitis to prevent the spread of the infection only in acute apical abscesses with systemic involvement, and in progressive and persistent infections. Medically compromised patients are more susceptible to complication arising from endodontic infections. Thus, antibiotics should be considered in patients having systemic diseases with compromised immunity and in patients with a localized congenital or acquired altered defence capacity, such as patients with infective endocarditis, prosthetic cardiac valves, or with recent prosthetic joint replacement. Although penicillin VK, possibly combined with metronidazole to cover anaerobic strains, is still effective in most cases, amoxicillin (alone or together with clavulanic acid) is recommended because of better absorption and lower risk of side effects. In case of confirmed penicillin allergy, lincosamides, such as clindamycin, are the drug of choice.

Conflict of Interest

The authors have stated explicitly that there is no conflict of interests in connection with this article.

REFERENCES

- [1] Sundquist, G. "Taxonomy, ecology and pathogenicity of the root canal flora." *Oral Surgery Oral Medicine Oral Pathology*, vol. 78, 1994, pp. 522–530.
- [2] Safavi, K.E. *et al.* "Root canal dentinal tubule disinfection." *Journal of Endodontics*, vol. 16, 1990, pp. 207–210.
- [3] Abbott, P.V. "Selective and intelligent use of antibiotics in endodontic." *Australian Endodontic Journal*, vol. 26, 2000, pp. 30–39.
- [4] Miles, M. "Anaesthetics, analgesics, antibiotics and endodontic." *Dental Clinics of North America*, vol. 28, 1984, pp. 865–882.
- [5] Gilad, J.Z. *et al.* "Development of a clindamycin impregnated fiber as an intercanal medication in endodontic therapy." *Journal of Endodontics*, vol. 25, 1999, pp. 722–727.
- [6] Lindblad, W.J. "Considerations for determining if a natural product is an effective wound-healing agent." *International Journal of Lower Extremity Wounds*, vol. 7, 2008, pp. 75–81.
- [7] Forrest, R.D. "Early history of wound treatment." *Journal of the Royal Society of Medicine*, vol. 75, 1982, pp. 198–205.
- [8] Molan, P.C. "Honey as a topical antibacterial agent for treatment of infected wounds." *Nursing Times*, vol. 49, 2001, pp. 96.
- [9] Foster, W. and Raoult, A. "Early descriptions of antibiosis." *Journal of the Royal College of General Practitioners*, vol. 24, 1974, pp. 889–894.
- [10] Landsberg, H. "Prelude to the discovery of penicillin." *Isis*, vol. 40, 1949, pp. 225–227.
- [11] Waksman, S.A. "What is an antibiotic or an antibiotic substance?" *Mycologia*, vol. 39, 1947, pp. 565–569.
- [12] Grossman, L.I. "Polyantibiotic treatment of pulpless teeth." *Journal of the American Dental Association*, vol. 43, 1951, pp. 265–278.
- [13] Mohammadi, Z. "An update on the antibiotic-based root canal irrigation solutions." *Iranian Endodontic Journal*, vol. 3, 2008, pp. 1–7.
- [14] Abbott, P.V. *et al.* "Antibiotics and endodontics." *Australian Dental Journal*, vol. 35, 1990, pp. 50–60.
- [15] Grossman, L.I. "Polyantibiotic treatment of pulpless teeth." *Journal of the American Dental Association*, vol. 43, 1951, pp. 265–278.
- [16] Gerding, D.E. "Antimicrobial treatment." In: Olmsted, R.N., ed. *APIC Infection Control and Applied Epidemiology: Principles and Practice*. Mosby-Year Book, 1996, pp. 521–526.
- [17] Titsas, A. and Ferguson, M.M. "Concepts for the prophylaxis of infective endocarditis in dentistry." *Australian Dental Journal*, vol. 46, 2001, pp. 220–225.
- [18] Oliver, R. *et al.* "Penicillins for the prophylaxis of bacterial endocarditis in dentistry." *The Cochrane Database of Systematic Reviews*, 2004, pp. 7–20.
- [19] Torabinejad, M. *et al.* "A new solution for the removal of smear layer." *Journal of Endodontics*, vol. 29, no. 3, 2003, pp. 170–175.
- [20] Glauser, M.P. *et al.* "Successful single dose amoxicillin prophylaxis against experimental streptococcal endocarditis: evidence for two mechanisms of protection." *Journal of Infectious Diseases*, vol. 14, 1983, pp. 568–575.
- [21] Rise, E. *et al.* "Reduction of bacteraemia after oral manipulations." *Archives of Otolaryngology*, vol. 90, 1969, pp. 198–201.
- [22] Scopp, I.W. and Orvieto, L.D. "Gingival degerming by povidone-iodine irrigation: bacteraemia reduction in extraction procedures." *Journal of the American Dental Association*, vol. 83, 1971, pp. 1294–1296.
- [23] MacFarlane, T.W. *et al.* "Postextraction bacteraemia: role of antiseptics and antibiotics." *British Dental Journal*, vol. 156, 1984, pp. 179–181.
- [24] Slattery, J.T. *et al.* "The complex interaction between ethanol and acetaminophen." *Clinical Pharmacology and Therapeutics*, vol. 60, 1996, pp. 241.
- [25] Carnes, P.L. *et al.* "Change in pain threshold to sharp pain by meperidine, naproxen, and acetaminophen as determined by electric pulp testing." *Anesthesia Progress*, vol. 45, 1998, pp. 139.
- [26] Slots, J. "Selection of antimicrobial agents in periodontal therapy." *Journal of Periodontal Research*, vol. 37, 2002, pp. 389–398.
- [27] Kuriyama, T. *et al.* "Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics." *Oral Microbiology and Immunology*, vol. 22, 2007, pp. 285–288.
- [28] Stein, G.E. *et al.* "Human serum activity of telithromycin, azithromycin and amoxicillin/clavulanate against common aerobic and anaerobic respiratory pathogens." *International Journal of Antimicrobial Agents*, vol. 29, 2007, pp. 39–43.
- [29] Gomes, B.P. *et al.* "Analysis of the antimicrobial susceptibility of anaerobic bacteria isolated from endodontic infections in Brazil during a period of nine years." *Journal of Endodontics*, vol. 37, 2011, pp. 1058–1062.
- [30] Gordon, D. "Amoxicillin-clavulanic acid (co-amoxiclav)." In: Grayson, M.L. *et al.*, eds. *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal, Antiparasitic and Antiviral Drugs*. Hodder Arnold/ASM Press, 2010, pp. 193–194.
- [31] American Association of Endodontists. "Prescription for the future: responsible use of antibiotics in endodontic therapy." *AAE Endodontics Colleagues for Excellence*, 1999, pp. 1–8.

- [32] U.S. National Library of Medicine. "Penicillin V potassium tablet: drug label sections." *DailyMed*, 2006.
- [33] Baumgartner, J.C. and Xia, T. "Antibiotic susceptibility of bacteria associated with endodontic abscesses." *Journal of Endodontics*, vol. 29, 2003, pp. 44–47.
- [34] Warnke, P.H. *et al.* "Penicillin compared with other advanced broad spectrum antibiotics regarding antibacterial activity against oral pathogens isolated from odontogenic abscesses." *Journal of Cranio-Maxillofacial Surgery*, vol. 36, 2008, pp. 462–467.
- [35] Pallasch, T.J. "Global antibiotic resistance and its impact on the dental community." *Journal of the California Dental Association*, vol. 28, 2000, pp. 215–233.
- [36] Khemaaleelakul, S. *et al.* "Identification of bacteria in acute endodontic infections and their antimicrobial susceptibility." *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontology*, vol. 94, 2002, pp. 746–755.
- [37] Macy, E. and Ngor, E.W. "Safely diagnosing clinically significant penicillin allergy using only penicilloyl-polylysine, penicillin, and oral amoxicillin." *Journal of Allergy and Clinical Immunology: In Practice*, vol. 1, 2013, pp. 258–263.
- [38] Macy, E. "Penicillin and beta-lactam allergy: epidemiology and diagnosis." *Current Allergy and Asthma Reports*, vol. 14, 2014, pp. 476.
- [39] Macy, E. "Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs." *Current Opinion in Allergy and Clinical Immunology*, vol. 15, 2015, pp. 308–313.
- [40] Baumgartner, J.C. and Smith, J.R. "Systemic antibiotics in endodontic infections." In: Fouad, A., ed. *Endodontic Microbiology*. Wiley-Blackwell, 2009.
- [41] Skučaitė, N. *et al.* "Antibiotic prescription for the treatment of endodontic pathology: a survey among Lithuanian dentists." *Medicina*, vol. 46, 2010, pp. 806–813.
- [42] Drugs.com. "Clindamycin dosage." 2016.
- [43] Moore, P.A. "Dental therapeutic indications for the newer long-acting macrolide antibiotics." *Journal of the American Dental Association*, vol. 130, 1999, pp. 1341–1343.
- [44] Pallasch, T.J. "How to use antibiotics effectively." *Journal of the California Dental Association*, vol. 21, 1993, pp. 46–50.
- [45] Fazakerley, M.W. *et al.* "A comparative study of cephadrine, amoxycillin and phenoxymethyl penicillin in the treatment of acute dentoalveolar infection." *British Dental Journal*, vol. 174, 1993, pp. 359–363.
- [46] Longman, L.P. and Martin, M.V. "The use of antibiotics in the prevention of post-operative infection: a re-appraisal." *British Dental Journal*, vol. 170, 1991, pp. 257–262.
- [47] Wilson, W. *et al.* "Prevention of infective endocarditis: guidelines from the American Heart Association." *Journal of the American Dental Association*, vol. 138, 2007, pp. 739–760.
- [48] Richey, R. *et al.* "Prophylaxis against infective endocarditis: summary of NICE guidance." *British Medical Journal*, vol. 336, 2008, pp. 770–771.
- [49] Austin, D.J. *et al.* "The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance." *Proceedings of the National Academy of Sciences of the United States of America*, vol. 96, 1999, pp. 1152–1156.
- [50] Andersson, D.I. and Hughes, D. "Persistence of antibiotic resistance in bacterial populations." *FEMS Microbiology Reviews*, vol. 35, 2011, pp. 901–911.
- [51] Lockhart, P.B. *et al.* "The evidence base for the efficacy of antibiotic prophylaxis in dental practice." *Journal of the American Dental Association*, vol. 138, 2007, pp. 458–474.
- [52] Schwartzberg, L.S. "Neutropenia: etiology and pathogenesis." *Clinical Cornerstone*, vol. 8, no. Suppl. 5, 2006, pp. S5–S11.
- [53] Lo Schiavo, A. *et al.* "Locus minoris resistentiae: an old but still valid way of thinking in medicine." *Clinics in Dermatology*, vol. 32, 2014, pp. 553–556.
- [54] Lacassin, F. *et al.* "Procedures associated with infective endocarditis in adults. A case control study." *European Heart Journal*, vol. 16, 1995, pp. 1968–1974.
- [55] Strom, B.L. *et al.* "Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study." *Annals of Internal Medicine*, vol. 129, 1998, pp. 761–769.
- [56] Richey, R., Wray, D. and Stokes, T. "Prophylaxis against infective endocarditis: summary of NICE guidance." *British Medical Journal*, vol. 336, 2008, pp. 770–771.
- [57] Nishimura, R.A. *et al.* "ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis." *Circulation*, vol. 118, 2008, pp. 887–896.
- [58] NICE. "Prophylaxis against infective endocarditis." NICE, 2008.
- [59] Dayer, M.J. *et al.* "Incidence of infective endocarditis in England, 2000–13: a secular trend, interrupted time-series analysis." *The Lancet*, vol. 385, 2015, pp. 1219–1228.
- [60] Thornhill, M.H. *et al.* "A change in the NICE guidelines on antibiotic prophylaxis." *British Dental Journal*, vol. 221, 2016, pp. 112–114.
- [61] European Society of Cardiology. "ESC Guidelines for the management of infective endocarditis." *European Heart Journal*, vol. 36, 2015, pp. 3075–3123.
- [62] Seymour, R.A., Whitworth, J.M. and Martin, M. "Antibiotic prophylaxis for patients with joint prostheses - still a dilemma for dental practitioners." *British Dental Journal*, vol. 194, 2003, pp. 649–653.
- [63] Olsen, I., Snorrason, F. and Lingaas, E. "Should patients with hip joint prosthesis receive antibiotic prophylaxis before dental treatment?" *Journal of Oral Microbiology*, vol. 2, 2010.
- [64] Berbari, E.F. *et al.* "Dental procedures as risk factors for prosthetic hip or knee infection: a hospital-based prospective case-control study." *Clinical Infectious Diseases*, vol. 50, 2010, pp. 8–16.
- [65] Kao, F.C. *et al.* "Prosthetic joint infection following invasive dental procedures and antibiotic prophylaxis in patients with hip or knee arthroplasty." *Infection Control and Hospital Epidemiology*, 2016.
- [66] Font-Vizcarra, L. *et al.* "Relationship between intraoperative cultures during hip arthroplasty, obesity, and the risk of early prosthetic joint infection: a prospective study of 428 patients." *International Journal of Artificial Organs*, vol. 34, 2011, pp. 870–875.
- [67] Waldman, B.J., Mont, M.A. and Hungerford, D.S. "Total knee arthroplasty infections associated with dental procedures." *Clinical Orthopaedics and Related Research*, vol. 343, 1997, pp. 164–172.
- [68] LaPorte, D.M., Waldman, B.J., Mont, M.A. and Hungerford, D.S. "Infections associated with dental procedures in total hip arthroplasty." *Journal of Bone and Joint Surgery*, vol. 81, 1999, pp. 56–59.
- [69] Tolentino, E.S. *et al.* "Oral adverse effects of head and neck radiotherapy: literature review and suggestion of a clinical oral care guideline for irradiated patients." *Journal of Applied Oral Science*, vol. 19, 2011, pp. 448–454.

- [70] NIDCR. "Oral Complications of Cancer Treatment: What the Oral Health Team Can Do." NIDCR, 2009.
- [71] Dannemann, C. *et al.* "Jaw osteonecrosis related to bisphosphonate therapy: a severe secondary disorder." *Bone*, vol. 40, 2007, pp. 828–834.
- [72] Montefusco, V. *et al.* "Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates." *Leukemia and Lymphoma*, vol. 49, 2008, pp. 2156–2162.