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REVIEW

Antibiotics in Endodontics: a review

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Abstract

Segura-Egea JJ, Gould K, Hakan Şen B, Jonasson P, Cotti E, Mazzoni A, Sunay H, Tjäderhane L, Dummer PMH. Antibiotics in Endodontics: a review. *International Endodontic Journal*.

The overuse of antibiotics and the emergence of antibiotic-resistant bacterial strains is a global concern. This concern is also of importance in terms of the oral microbiota and the use of antibiotics to deal with oral and dental infections. The aim of this paper was to review the current literature on the indications and use of antibiotics and to make recommendations for their prescription in endodontic patients. Odontogenic infections, including endodontic infections, are polymicrobial, and in most cases, the prescription of antibiotics is empirical. This has led to the increasing use of broad-spectrum antibiotics even in cases where antibiotics are not indicated, such as symptomatic irreversible pulpitis, necrotic pulps and localized acute apical abscesses. In case of discrete and localized swelling, the primary aim is to achieve drainage without additional antibiotics. Adjunctive antibiotic treatment may be necessary in the prevention of the spread of infection, in acute apical abscesses with systemic involvement and in progressive and persistent infections. Medically compromised patients are more susceptible to complication arising from odontogenic infections and antimicrobials have a more specific role in their treatment. Therefore, antibiotics should be considered in patients having systemic diseases with compromised immunity or in patients with a localized congenital or acquired altered defence capacity, such as patients with infective endocarditis, prosthetic cardiac valves or recent prosthetic joint replacement. Penicillin VK, possibly combined with metronidazole to cover anaerobic strains, is still effective in most cases. However, 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.

Keywords: antibiotics, Endodontics.

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Introduction

There is international concern about the overuse of antibiotics and the emergence of antibiotic-resistant bacterial strains (Pallasch 2000). As dentists prescribe approximately 10% of antibiotics dispensed in primary care, it is important not to underestimate the potential contribution of the dental profession to the development of antibiotic-resistant bacteria (Cope *et al.* 2014). For example, in the UK, it has been reported that 40% of dentists prescribed antibiotics at least three times each week, and 15% prescribed antibiotics on a daily basis (Lewis 2008).

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Antibiotics do not reduce pain or swelling arising from teeth with symptomatic apical pathosis in the absence of evidence of systemic involvement (Fouad *et al.*1996, Henry *et al.* 2001, Keenan *et al.* 2006, Cope *et al.* 2014). Furthermore, one Cochrane systematic review has found no evidence to support the use of antibiotics for pain relief in irreversible pulpitis (Agnihotry *et al.* 2016). Thus, two systematic reviews (Matthews *et al.* 2003, Aminoshariae & Kulild 2016) concluded that infection must be systemic or the patient must be febrile or immunocompromised to justify the need for antibiotics (Mohammadi 2009). For these reasons, prescription of antibiotics by dentists should be limited (Rodriguez-Núñez *et al.* 2009).

Odontogenic infections, including endodontic infections, are polymicrobial involving a combination of gram-positive, gram-negative, facultative anaerobes and strict anaerobic bacteria (Siqueira & Roças 2014). When bacteria become resistant to antibiotics, they also gain the ability to exchange this resistance (Jungermann *et al.* 2001).

Antibiotic sensitivity of the bacteria found within the oral cavity is gradually decreasing, and a growing number of resistant strains are being detected, in particular *Porphyromonas* spp. and *Prevotella* spp. (Bresco-Salinas *et al.* 2006). However, the phenomenon has also been reported for alpha haemolytic streptococci ('*Streptococcus viridans*') and for drugs such as macrolides, penicillin and clindamycin (Aracil *et al.* 2001, Groppo *et al.* 2004).

Inappropriate use of antibiotics not only drives antibiotic resistance and misuses resources but also increases the risk of potentially fatal anaphylactic reactions and exposes people to unnecessary side effects (Gonzales *et al.* 2001, Costelloe *et al.* 2010, Cope *et al.* 2014). In addition, antibiotic prescribing for common medical problems increases patient expectations for antibiotics, leading to a vicious cycle of increased prescribing in order to meet expectations (Cope *et al.* 2014).

In dentistry, antibiotic prescription is empirical because the dentist does not know what microorganisms are responsible for the infection, as samples from the root canal or periapical region are not commonly taken and analysed. Thus, based on clinical and bacterial epidemiological data, the microorganisms responsible for the infections can only be suspected, and treatment is decided on a presumptive basis with broad-spectrum antibiotics often being prescribed (Poveda Roda *et al.* 2007).

Antibiotic prescribing in Endodontics within Europe

Since the 1970s, antibiotic prescribing in dentistry and, specifically, in endodontics, has mostly been analysed by mean of cross-sectional observational studies conducted using surveys. The survey instrument has historically been successful in obtaining pertinent information on the practice of endodontics. Questions are designed to collect a variety of data on the types of antibiotics used and the prescribing habits of dentists/endodontists as determined by their age, gender, academic degree, area of the country and percentage of time assigned to endodontics in their overall dental practice. In these surveys, the overall response rate ranged between 30% and 45% (Rodriguez-Núñez *et al.* 2009, Segura-Egea *et al.* 2010).

In Europe, several surveys have studied the pattern of antibiotic prescribing in the treatment of endodontic diseases (Table 1). Amoxicillin was the first-choice antibiotic prescribed in endodontic infection in most of the surveys (Palmer *et al.* 2000, Dailey & Martin 2001, Tulip & Palmer 2008, Mainjot *et al.* 2009, Rodriguez-Núñez *et al.* 2009, Segura-Egea *et al.* 2010, Skučaitė *et al.* 2010, Kaptan *et al.* 2013, Peric *et al.* 2015). Only in Turkey was it reported that ampicillin was the first-choice antibiotic for endodontic infections (Kandemir & Ergül 2000). In allergic patients, clindamycin (Rodriguez-Núñez *et al.* 2009, Segura-Egea *et al.* 2010, Kaptan *et al.* 2013, Peric *et al.* 2015) and erythromycin (Mainjot *et al.* 2009, Dailey & Martin 2001) were the preferred antibiotics.

Pulpal and periapical conditions in which antibiotics were prescribed varied amongst the studies. Mainjot *et al.* (2009) analysed antibiotic prescribing in dental practice within Belgium, finding that antibiotics were often prescribed in the absence of fever (92.2%) and without any local dental treatment (54.2%). Antibiotics were prescribed to 63.3% of patients with a periapical abscess and 4.3% of patients with pulpitis. Skučaitė *et al.* (2010) analysed the pattern of antibiotic prescribing for the treatment of endodontic pathosis amongst Lithuanian dentists. The majority of the respondents (84%) reported symptomatic apical periodontitis with periostitis (inflammation of the periosteum) being a clear indication for the prescription of antibiotics, but nearly 2% of the respondents reported prescribing antibiotics in cases of symptomatic pulpitis. Rodriguez-Núñez *et al.* (2009) studied the antibiotic-prescribing habits of

active members of the Spanish Endodontic Society (AEDE). For cases of irreversible pulpitis, 40% of respondents prescribed antibiotics. For the scenario of a necrotic pulp, acute apical periodontitis and no swelling, 53% prescribed antibiotics. Segura-Egea *et al.* (2010) analysed the use of antibiotics in the treatment of endodontic infections amongst the members of the Spanish Oral Surgery Society (SECIB). For cases of irreversible pulpitis, 86% of respondents prescribed antibiotics. For the scenario of a necrotic pulp, acute apical periodontitis and no swelling, 71% prescribed antibiotics. Thus, many European dentists are prescribing antibiotics inappropriately to treat minor infections.

Systemic use of antibiotics in endodontic infections

In addition to normal endodontic procedures, adjunctive strategies may be needed in cases where there is abscess formation. The primary aim should be to achieve drainage (Abbott 2000, Baumgartner & Smith 2009, Mohammadi 2009). Where there is discrete and localized swelling, drainage by itself is considered sufficient without the need for additional medication (Matthews *et al.* 2003). Antibiotics are unnecessary in irreversible pulpitis, necrotic pulps and localized acute apical abscesses (Fouad *et al.* 1996, Nagle *et al.* 2000, Agnihotry *et al.* 2016). Lack of blood circulation in the root canal in these scenarios prevents antibiotics reaching the area; that is, they are ineffective in eliminating the microorganisms. Cope *et al.* (2014) evaluated the effects of systemic antibiotics provided with or without surgical intervention, with or without analgesics, for symptomatic apical periodontitis or acute apical abscess in adults in a recent Cochrane review. They concluded that there was very low-quality evidence, which was insufficient to determine the effects of systemic antibiotics in adults with symptomatic apical periodontitis or acute apical abscess.

On the other hand, antibiotics are useful adjuncts in specific cases as they assist in the prevention of the spread of infection (Zeitoun & Dhanarajani 1995). Clearly, the clinician must identify these specific cases correctly and caution must be exercised both during the prescription of specific antibiotics and the duration of administration. Table 2 summarizes cases where adjunctive antibiotic treatment is indicated during endodontic treatment, as well as cases in which antibiotics are not indicated.

The clinician must be cautious about the development of cellulitis in cases of acute apical abscess in which the transudate and exudate spread via interstitial and tissue spaces. In such cases, incision for drainage is of utmost importance, as it will enhance the diffusion of the antibiotic into the affected area. Thus, the advantages of drainage are twofold: both for the relief of the patient by the removal of toxic products and for the antibiotic to penetrate into the infected space more readily (Baumgartner & Smith 2009). In case of successful drainage, antibiotics offer little help, and their use should be reserved for patients with acute AP and systemic symptoms or to medically challenged or immunocompromised patients (Matthews *et al.* 2003).

The selection of a specific antibiotic is generally based on empirical criteria and on the types of bacteria most frequently isolated from periapical lesions, which are often facultative or anaerobic in nature

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 *et al.* (2000)	UK	General Practitioner	Amoxicillin	Penicillin VK	Metronidazole	5 (3–10)[a]
Kandemir & Ergül (2000)	Turkey	General Practitioner	Ampicillin	Amoxicillin	–	–
Dailey & Martin (2001)	UK	General Practitioner	Amoxicillin	Amoxicillin / Metronidazole	–	–
Tulip & Palmer (2008)	UK	General Practitioner	Amoxicillin	Metronidazole	–	–
Rodriguez-Núñez *et al.* (2009)	Spain	Endodontist	Amoxicillin	Metronidazole / Spiramycin	Clindamycin	6.8 ± 1.8[b]
Mainjot *et al.* (2009)	Belgium	General Practitioner	Amoxicillin	Clindamycin	Erythromycin	–
Skučaitė *et al.* (2010)	Lithuania	General Practitioner	Amoxicillin	Penicillin VK	–	
Segura-Egea *et al.* (2010)	Spain	Dental Surgeon	Amoxicillin	Clindamycin	Clindamycin	7.0 ± 1.0[b]
Kaptan *et al.* (2013)	Turkey	General Practitioner	Amoxicillin	Clindamycin	Clindamycin	
Peric *et al.* (2015)	Croatia	Dental Surgeon	Amoxicillin	Clindamycin	Clindamycin	6.4 ± 1.6[b]

Duration: [a]Range; [b]Mean days ± standard deviation.

Table 2 Indications for antibiotics as an adjunct during endodontic therapies (references in the text)

Pulp/Periapical condition	Clinical and radiographic data	Antibiotics as adjunct
Symptomatic irreversible pulpitis	• Pain • No others symptoms and signs of infection	NO
Pulp necrosis	• Nonvital teeth • Widening of periodontal space	NO
Acute apical periodontitis	• Pain • Pain to percussion and biting • Widening of periodontal space	NO
Chronic apical abscess	• Teeth with sinus tract • Periapical radiolucency	NO
Acute apical abscess with no systemic involvement	• Localized fluctuant swellings	NO
Acute apical abscess in medically compromised patients	• Localized fluctuant swellings • Patient with systemic disease causing impaired immunologic function	YES
Acute apical abscess with systemic involvement	• Localized fluctuant swellings • Elevated body temperature (>38 °C) • Malaise • Lymphadenopathy • Trismus	YES
Progressive infections	• Rapid onset of severe infection (less than 24 h) • Cellulitis or a spreading infection • Osteomyelitis	YES
Persistent infections	• Chronic exudation, which is not resolved by regular intracanal procedures and medications	YES

(Khemaaleelakul *et al.* 2002, Hargreaves & Cohen 2011). Culturing for identification and antibiotic susceptibility testing are advised especially for medically compromised and immunocompromised patients. Even then, empirical administration should be initiated as the identification and susceptibility tests may take some time to report back, ranging from a few days to several weeks. The sampling should be undertaken meticulously to prevent contamination. Both the collection and transfer of samples to the laboratory must be made under strict measures in order to prevent misleading results (Nagle *et al.* 2000, Baumgartner & Smith 2009).

Systemic antibiotic use in the treatment of traumatic injuries of the teeth

Dental injuries are common especially amongst younger individuals. In these cases, prevention of bacterial contamination is of great concern as the prognosis may be dramatically affected, particularly when bacteria are able to access the site of injury and compromise healing. Inflammatory root resorption is one of the most undesirable complications associated with traumatic injuries. Thus, exclusion or limitation of the bacterial load during the healing phase is a logical approach to obtain the best outcomes in the management of traumatic injuries (Andreasen *et al.* 2006). From current knowledge and based on the International Association of Dental Traumatology (IADT) guidelines (Andersson *et al.* 2012), the following recommendations can be made in terms of antibiotic administration following traumatic dental injuries (Table 3).

Luxation injuries of the permanent dentition

IADT guidelines (http://dentaltraumaguide.org/) do not recommend the use of systemic antibiotics in the management of luxation injuries or in teeth with root fractures. On the other hand, antibiotic administration might be indicated at the discretion of the clinician when the injury is accompanied by soft tissue trauma requiring intervention. In some cases, the medical status of the patient may also require antibiotic administration (Diangelis *et al.* 2012).

Replantation of avulsed teeth

Current guidelines recommend systemic antibiotic therapy for patients with avulsion of a permanent

tooth, which is replanted (Hinckfuss & Messer 2009). The IADT guidelines state that although the significance of systemic antibiotic administration has not yet been demonstrated by clinical studies, positive effects have been shown in periodontal and pulpal healing in experimental studies, specifically using topical application (Andersson *et al.* 2012).

In conclusion, systemic antibiotic administration, in compliance with the age and weight of the patient, may be a useful adjunct for avulsed permanent teeth. On the other hand, in traumatic injuries other than avulsion, such as fracture or luxation injuries, antibiotic administration does not appear to offer any additional advantage unless the patient's medical status or the degree of soft tissue injury necessitate its application.

Table 3 Indications for systemic antibiotics as adjuncts during the treatment of traumatic injuries of the teeth (references in the text)

Traumatic injury	Systemic antibiotics as adjunct	Type of antibiotic
Tooth fracture	NO	–
Concussion, Subluxation	NO	–
Luxation injuries of permanent dentition	NO	–
Extrusion	NO	–
Replantation of avulsed teeth	YES	Tetracycline, Doxycycline

Topical antibiotic use in endodontics

The use of topical antibiotics has been proposed for several endodontic treatments.

Pulp capping

Dental pulp capping procedures include the application of a protective agent to an exposed pulp (direct capping) or retaining a thin layer of dentine over a nearly exposed pulp (indirect capping) in order to allow the pulp to recover and maintain its normal status and function (Miyashita *et al.* 2007). Although several clinicians and researchers have used topical antibiotics in pulp capping (Cowan 1966, Mjör & Ostby 1966, Clarke 1971, Lakshmanan 1972, McWalter *et al.* 1973, Soldati 1974, Abbott *et al.* 1989, Yoshiba *et al.* 1995, Cannon *et al.* 2008), there is no scientific evidence to support the use of antibiotics in pulp capping procedures. On the contrary, MTA or other calcium silicate-based materials should be used once the cause of the disease (e.g. caries) has been addressed (Farsi *et al.* 2006, Bogen *et al.* 2008, Li *et al.* 2015).

Root canal treatment

The risk of adverse effects following systemic application and the ineffectiveness of systemic antibiotics in some pulpal and periapical conditions has led to the use of locally applied antibiotics in root canal treatment, that is within the canal system (Mohammadi & Abbott 2009). The first reported locally used antibiotic product was a polyantibiotic paste containing penicillin, bacitracin, streptomycin and caprylate sodium (Grossman 1951).

Taking into account that endodontic infections are polymicrobial, tetracyclines (tetracycline HCl, minocycline, demeclocycline, doxycycline), a group of broad-spectrum antibiotics that are effective against a wide range of microorganisms, have been proposed as intracanal topical antibiotics. Sato *et al.* (1996) demonstrated the penetration through dentine and the antibacterial efficacy of a mixture of minocycline, a tetracycline, with ciprofloxacin and metronidazole, placed in root canals previously irrigated ultrasonically. Molander *et al.* (1990) demonstrated that intracanal clindamycin offers no advantage over conventional calcium hydroxide root canal dressing. BioPure MTAD (Dentsply Sirona, Salzburg, Austria), a mixture of doxycycline, citric acid and a detergent (Tween 80), has been proposed as a final irrigant because of its numerous properties: antimicrobial activity, smear layer- and pulp-dissolving capability, effect on dentine and adhesion, and biocompatibility (Torabinejad *et al.* 2003). However, microorganisms isolated from root canals have resistance against this group of antibiotics (Jungermann *et al.* 2001, Skučaitė *et al.* 2010, Al-Ahmad *et al.* 2014), and tetracyclines may promote fungal growth (MacNeill *et al.* 1997).

Abbott *et al.* (1990) demonstrated that when placed in the root canal, the concentration and effectiveness of 3.2% demeclocycline (Ledermix, Lederle Pharmaceuticals, Wolfratshausen, Germany) were significantly reduced in peripheral dentine and in the apical third over time. In addition to limited antimicrobial activity (Abbott *et al.* 1990), tetracyclines cause discolouration of teeth when used as a medicament in root canals (Chen *et al.* 2012). Septomixine forte (Septodont, Saint-Maur-des-fossé, France) is

another commercial product for intracanal use. It contains two antibiotics, neomycin and polymyxin B sulphate, but the effect against endodontic flora is not better than with calcium hydroxide (Tang *et al.* 2004, Chu *et al.* 2006).

The use of topical antibiotics in root canal treatment has also been proposed to prevent or reduce postoperative symptoms. However, antibiotics do not reduce the pain or swelling arising from teeth with symptomatic apical pathosis (Keenan *et al.* 2006, Cope *et al.* 2014).

In summary, use of topical antibiotics during root canal treatment is not supported by the evidence.

Regenerative endodontic procedures

Murray *et al.* (2007) defined regenerative endodontic procedures (REPs) as biologically based procedures designed to replace damaged structures, including dentine and root structures, as well as cells of the pulp–dentine complex. In immature teeth with necrotic pulps and open apices, REPs promote root development and apical closure. Most REPs include minimal-to-no mechanical debridement (Diogenes *et al.* 2013), relying on chemical debridement and on the use of intracanal medicaments to achieve disinfection. Therefore, intracanal medicaments have been used in almost all published case reports (Kontakiotis *et al.* 2015).

Antibiotics used in regenerative endodontic procedures

The antibiotic mixture composed of ciprofloxacin, metronidazole and minocycline (100 μg mL^{-1} of each antibiotic, 300 μg mL^{-1} of mixture) known as triple antibiotic paste (TAP) or '3mix' has to date been the most widely used intracanal medicament in REPs (Diogenes *et al.* 2013).

The nitroimidazole compound metronidazole is known for its broad spectrum and strong antibacterial activity against anaerobic cocci, as well as gram-negative and gram-positive bacilli. Metronidazole permeates bacterial cell membranes, reaches the nuclei and binds to the DNA, disrupting its helical structure, causing cell death. Metronidazole has excellent activity against anaerobes isolated from odontogenic abscesses (Roche & Yoshimori 1997). Moreover, the use of metronidazole has been advocated because of its low induction of bacterial resistance (Slots 2002).

Minocycline is a bacteriostatic and broad-spectrum antimicrobial. It is effective against both gram-positive and gram-negative microorganisms, including most spirochetes and many anaerobic and facultative bacteria. Minocycline has been used in periodontal therapy, being available in many topical forms (Angaji *et al.* 2010).

The synthetic fluoroquinolone ciprofloxacin has very potent activity against gram-negative pathogens, but its activity is limited against gram-positive bacteria, and most anaerobic bacteria are resistant to ciprofloxacin. Consequently, ciprofloxacin is often combined with metronidazole in the treatment of mixed infections.

Side effects of antibiotics used in regenerative endodontic procedures

The use of antibiotics as intracanal dressings in REP may promote several side effects. A problem that often accompanies the intracoronal use of TAP containing minocycline is dentine discolouration (Hoshino *et al.* 1996, Sato *et al.* 1996, Kim *et al.* 2010, Miller *et al.* 2012, Rodríguez-Benítez *et al.* 2015). Thibodeau & Trope (2007) suggested substituting minocycline for cefaclor in the tri-antibiotic formula to avoid dentine discolouration, and Miller *et al.* (2012) confirmed that the incorporation of cefaclor into TAP, instead of minocycline, avoided discolouration. The recent review and ESE position statement on revitalization procedures advocate the use of calcium hydroxide instead of antibiotics to avoid discolouration (ESE 2016, Galler 2016).

Antibiotics and dental pulp stem cells

The preservation of host residual cells is essential for favourable REP outcomes. Stem cells must survive to contribute to tissue regeneration (Diogenes *et al.* 2013). The mixture of ciprofloxacin, metronidazole and minocycline has been demonstrated to be well tolerated by vital pulp tissues (Ayukawa 1994, Paryani & Kimi 2013). Moreover, the effect of TAP on subcutaneous tissue of rats over different time periods has been evaluated, concluding that it is biocompatible (Gomes-Filho *et al.* 2012, Wigler *et al.* 2013). The TAP concentration used in regenerative endodontic procedures (100 μg mL^{-1} each antibiotic) is highly effective against endodontic bacteria and is nontoxic to stem cells of the apical papilla (SCAP) (Takushige *et al.* 2004).

Tooth avulsion

Topical antibiotic application on a tooth to be replanted after avulsion is also advocated to enhance

healing. Moreover, the use of topical antibiotics has been reported to be more beneficial compared with systemic antibiotics in avulsion cases (Hinckfuss & Messer 2009). This approach was supported by a study using replanted monkey teeth where inflammatory root resorption was significantly arrested by the use of topical doxycycline (Cvek *et al.* 1990).

There is evidence that antibiotics may be important to control infection and to reduce the risk of inflammatory resorption (Hammarström *et al.* 1986, Lee *et al.* 2001). As inflammatory root resorption is one of the major challenges faced by clinicians during the management of a replanted tooth, topical antibiotic administration might serve as a helpful means to eliminate this undesirable complication (Andersson *et al.* 2012). The IADT guidelines indicate that topical application of tetracyclines (minocycline or doxycycline, 1 mg per 20 mL of saline for 5 min) onto the root surface before reimplantation appears experimentally to have a beneficial effect, increasing the chance of pulpal space revascularization and periodontal healing in avulsed immature teeth with open apices (Andersson *et al.* 2012).

Types of antibiotics and recommended dosages in endodontics

As has been commented previously, amoxicillin, alone or in combination with clavulanic acid, is the preferred prescribed antibiotic in endodontic infections with systemic effects in all surveys carried out in Europe (Tulip & Palmer 2008, Mainjot *et al.* 2009, Rodriguez-Núñez *et al.* 2009, Segura-Egea *et al.* 2010, Skučaitė *et al.* 2010, Kaptan *et al.* 2013) (Table 1).

Amoxicillin is a moderate-spectrum, bacteriolytic, β-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 (Slots 2002). However, amoxicillin is susceptible to degradation by β-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 (Kuriyama *et al.* 2007, Stein *et al.* 2007) and low resistance of bacteria cultivated from root canal samples (Gomes *et al.* 2011). 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 immunocompromised patients or those infections that have not responded to first-line antimicrobial therapy when provided in conjunction with operative treatment (Gordon 2010).

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 4). 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 (American Association of Endodontists 1999). 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 important than slightly better antimicrobial spectrum, amoxicillin is better absorbed, and can therefore be use in a lower dose and may thus reduce the gastrointestinal side effects. On the other hand, penicillin-induced diarrhoea may even further reduce

Table 4 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	1000 mg	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

[a]If 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.
[b]If the patient is allergic to penicillin.

antibiotic absorption, decreasing antibiotic levels in circulation and in the infected area.

Penicillin V is a narrow-spectrum antibiotic for infections caused by aerobic gram-negative cocci, facultative and anaerobic microorganisms (U.S. NLM 2006). 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 (U.S. NLM 2006).

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 (Baumgartner & Xia 2003).

In a clinical study with 94 patients with abscesses (Warnke *et al.* 2008), 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.

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 (Pallasch 2000) (Table 4). Following debridement of the root canal system and drainage, significant improvement should be seen within 48–72 h. However, if penicillin V therapy is ineffective, another antibiotic should be selected, ideally following culture and sensitivity testing. Clindamycin is a good alternative (Khemaaleelakul *et al.* 2002). 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 (Macy & Ngor 2013). Unverified penicillin allergy is being increasingly recognized as a significant public health problem (Macy 2014, 2015). In patients with a confirmed penicillin allergy history, the clinician can switch to other antimicrobial agents such as clindamycin, metronidazole and clarithromycin or azithromycin (Baumgartner & Smith 2009, Skučaitė *et al.* 2010). 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, that is 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 (Baumgartner & Smith 2009). The adult oral dosage is 600 mg loading dose followed by 300 mg every 6 h (Table 4, Drugs.com 2016).

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 (American Association of Endodontists (AAE) 1999). Because there are many bacteria resistant to metronidazole and it is not effective against aerobic and facultative bacteria (Khemaaleelakul *et al.* 2002, Baumgartner & Xia 2003), 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 (Baumgartner & Xia 2003). The adult oral dosage is 1000 mg loading dose followed by 500 mg every 6 h (Table 4).

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 (Moore 1999). 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 (Table 4; Drugs.com 2016).

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 (Pallasch 1993), there is a general tendency to administer an antibiotic for 3–7 days (Fazakerley *et al.* 1993) (Table 1). As prolonged antibiotic usage destroys the commensal flora in the oral cavity and other body sites and terminates colonization resistance (Longman & Martin 1991), 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 (American Association of Endodontists 1999). Fazakerley *et al.* (1993) and Martin *et al.* (1997) 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 chemomechanical 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 (Wilson *et al.* 2007, Richey *et al.* 2008). The risk of adverse reactions to antibiotics and increasing development of drug-resistant bacteria outweigh the benefits of prophylaxis for most patients (Austin *et al.* 1999, Andersson & Hughes 2011). Antibiotics should only be given prophylactically in cases where the benefit has been demonstrated or where consensus exists as to such use.

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 (Lockhart *et al.* 2007). However, there may be other patient groups in which antibiotic prophylaxis may be of benefit, but case–control studies or double-blinded studies with placebo have not been performed for ethical reasons.

Immunocompromised patients

Individuals who are immunocompromised 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 (1000–1500 μL^{-1}), moderate (500–1000 μL^{-1}) and severe (< 500 μL^{-1}). When neutrophil counts fall to < 500 μL^{-1}, endogenous microbial flora (e.g. in the mouth or gut) can cause infections (Schwartzberg 2006).

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 (Lo Schiavo *et al.* 2014). Infective endocarditis, a bacterial infection of the heart valves or the endothelium of the heart, is a typical case of *locus minoris resistentiae*. Individuals with certain pre-existing heart defects are considered at risk for developing endocarditis when a bacteraemia occurs. 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 (Lacassin *et al.* 1995, Strom *et al.* 1998, Wilson *et al.* 2007, Richey *et al.* 2008).

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 (Nishimura *et al.* 2008). 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 (NICE 2008). 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 (Dayer *et al.* 2015), 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 (Thornhill *et al.* 2016). 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 (European Society of Cardiology 2015).

The scientific evidence is insufficient to indicate providing antibiotic prophylaxis before dental treatment for healthy patients after prosthetic joint replacement (Seymour *et al.* 2003, Uckay *et al.* 2008, Olsen *et al.* 2010), 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 (Berbari *et al.* 2010, Kao *et al.* 2016). The joint guideline by American Academy of Orthopaedic Surgeons and American Dental

Association in 2012 (http://www.aaos.org/uploadedFiles/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 (Font-Vizcarra *et al.* 2011), as well as in patients with compromised host defence undergoing extensive dental procedures (Waldman *et al.* 1997, LaPorte *et al.* 1999). 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 (Berbari *et al.* 2010, Kao *et al.* 2016).

Jawbones exposed to high dose of radiation for cancer treatment in the head and neck results in lifelong

Table 5 Antibiotic prophylaxis for medically compromised patients (references in the text)

Patient group	Antibiotic	Route	Dose		Timing before procedure
			Adults	Children	
Standard general prophylaxis	Amoxicillin	PO	2 g	50 mg kg^{-1}	1 h
Unable to take oral medication	Ampicillin	IV o IM	2 g	50 mg kg^{-1}	Within 30 min
Allergic to penicillin	Clindamycin	PO	600 mg	20 mg kg^{-1}	1 h
	Cephalexin or cefadroxil	PO	2 g	50 mg kg^{-1}	1 h
	Azithromycin or clarithromycin	PO	500 mg	15 mg kg^{-1}	1 h
Allergic to penicillin / amoxicillin / ampicillin and unable to take oral medications	Clindamycin	IV	600 mg	20 mg kg^{-1}	Within 30 min
	Cefazolin	IV	1 g	25 mg kg^{-1}	Within 30 min

changes in microcirculation and are thus more susceptible to local infection-related complications (Tolentino Ede *et al.* 2011). Dental treatment with a risk to translocate infection to the bone in high-dose-exposed areas should be preceded by antibiotic prophylaxis (NIDCR 2009).

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 (Dannemann *et al.* 2007). Intravenous bisphosphonate treatment as an accompanying therapy for advanced tumour diseases warrants antibiotic prophylaxis in bone invasive procedures (Montefusco *et al.* 2008).

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 is presented in Table 5 as recommended by the AHA (Nishimura *et al.* 2008).

Conclusions

The use of systemic antibiotics in endodontics should be limited to specific cases so as to avoid their overprescription. 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 are no conflict of interests in connection with this article.

References

Abbott PV (2000) Selective and intelligent use of antibiotics in endodontics. *Australian Endodontic Journal* **26**, 30–9.

Abbott PV, Hume WR, Heithersay GS (1989) The release and diffusion through human coronal dentine *in vitro* of triamcinolone and demeclocycline from Ledermix paste. *Endodontics and Dental Traumatology* **5**, 92–7.

Abbott PV, Hume WR, Pearman JW (1990) Antibiotics and endodontics. *Australian Dental Journal* **3**, 50–60.

Agnihotry A, Fedorowicz Z, van Zuuren EJ, Farman AG, Al-Langawi JH (2016) Antibiotic use for irreversible pulpitis. *Cochrane Database Systematic Reviews* **2**: CD004969. doi: 10.1002/14651858.CD004969.pub4

Al-Ahmad A, Ameen H, Pelz K *et al.* (2014) Antibiotic resistance and capacity for biofilm formation of different bacteria isolated from endodontic infections associated with root-filled teeth. *Journal of Endodontics* **40**, 223–30.

American Association of Endodontists (AAE) (1999) Prescription for the future: responsible use of antibiotics in endodontic therapy. *AAE Endodontics Colleagues for Excellence* **1999**, 1–8.

Aminoshariae A, Kulild J (2016) Evidence-based recommendations for antibiotic usage for endodontic infections and pain: a systematic review. *Journal of the American Dental Association* **147**, 186–91.

Andersson DI, Hughes D (2011) Persistence of antibiotic resistance in bacterial populations. *Fems Microbiology Reviews* **35**, 901–11.

Andersson L, Andreasen JO, Day P *et al.* (2012) International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 2. Avulsion of permanent teeth. *Dental Traumatology* **28**, 88–96.

Andreasen JO, Bakland LK, Andreasen FM (2006) Traumatic intrusion of permanent teeth. Part 3. A clinical study of the effect of treatment variables such as treatment delay, method of repositioning, type of splint, length of splinting and antibiotics on 140 teeth. *Dental Traumatology* **22**, 99–111.

Angaji M, Gelskey S, Nogueira-Filho G, Brothwell DA (2010) Systematic review of clinical efficacy of adjunctive antibiotics in the treatment of smokers with periodontitis. *Journal of Periodontology* **81**, 1518–28.

Aracil B, Minambres M, Oteo J, Torres C, Gomez-Garces JL, Alos JI (2001) High prevalence of erythromycin-resistant and clindamycin-susceptible (M phenotype) viridans group streptococci from pharyngeal samples: a reservoir of mef genes in commensal bacteria. *Journal of Antimicrobial Chemotherapy* **48**, 592–4.

Austin DJ, Kristinsson KG, Anderson RM (1999) 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* **96**, 1152–6.

Ayukawa Y (1994) Pulpal response of human teeth to antibacterial biocompatible pulp capping agent-improvement of mixed drugs. *Japanese Journal of Conservative Dentistry* **37**, 643–51.

Baumgartner JC, Smith JR (2009) *"Systemic antibiotics in endodontic infections" in Endodontic Microbiology*; Ashraf Fouad. Iowa, USA: Wiley – Blackwell.

Baumgartner JC, Xia T (2003) Antibiotic susceptibility of bacteria associated with endodontic abscesses. *Journal of Endodontics* **29**, 44–7.

Berbari EF, Osmon DR, Carr A *et al.* (2010) Dental procedures as risk factors for prosthetic hip or knee infection: a hospital-based prospective case-control study. *Clinical Infectious Diseases* **50**, 8–16.

Bogen G, Kim JS, Bakland LK (2008) Direct pulp capping with mineral trioxide aggregate: an observational study. *Journal of the American Dental Association* **139**, 305–15.

Bresco-Salinas M, Costa-Riu N, Berini-Aytes L, Gay-Escoda C (2006) Susceptibilidad antibiótica de las bacterias causantes de infecciones odontogénicas. *Medicina Oral, Patología Oral y Cirugía Bucal* **11**, 51–6.

Cannon M, Cernigliaro J, Vieira A, Percinoto C, Jurado R (2008) Effects of antibacterial agents on dental pulps of monkeys mechanically exposed and contaminated. *Journal of Clinical Pediatric Dentistry* **33**, 21–8.

Chen BK, George R, Walsh LJ (2012) Root discolouration following short-term application of steroid medicaments containing clindamycin, doxycycline or demeclocycline. *Australian Endodontic Journal* **38**, 124–8.

Chu FC, Leung WK, Tsang PC, Chow TW, Samaranayake LP (2006) Identification of cultivable microorganisms from root canals with apical periodontitis following two-visit endodontic treatment with antibiotics/steroid or calcium hydroxide dressings. *Journal of Endodontics* **32**, 17–23.

Clarke NG (1971) The corticosteroid-antibiotic dressing as a capping for inflamed dental pulps. *Australian Endodontic Journal* **16**, 71–6.

Cope AL, Chestnutt IG (2014) Inappropriate prescribing of antibiotics in primary dental care: reasons and resolutions. *Primary Dental Care Journal* **3**, 33–7.

Cope A, Francis N, Wood F, Mann MK, Chestnutt IG (2014) Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults. *Cochrane Database Systematic Reviews* (6) CD010136.

Costelloe C, Metcalfe C, Lovering A, Mant D, Hay A (2010) Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *British Medical Journal* **340**, c2096.

Cowan A (1966) Treatment of exposed vital pulps with a corticosteroid antibiotic agent. *British Dental Journal* **120**, 521–32.

Cvek M, Cleaton-Jones P, Austin J, Lownie J, Kling M, Fatti P (1990) Effect of topical application of doxycycline on pulp revascularization and periodontal healing in reimplanted monkey incisors. *Endodontics and Dental Traumatology* **6**, 170–6.

Dailey YM, Martin MV (2001) Are antibiotics being used appropriately for emergency dental treatment? *British Dental Journal* **191**, 391–3.

Dannemann C, Gratz KW, Riener MO, Zwahlen RA (2007) Jaw osteonecrosis related to bisphosphonate therapy: a severe secondary disorder. *Bone* **40**, 828–34.

Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH (2015) Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. *Lancet* **385**, 1219–28.

Diangelis AJ, Andreasen JO, Ebeleseder KA *et al.* (2012) International Association of Dental Traumatology. International Association of Dental Traumatology guidelines for the management of traumatic dental injuries: 1. Fractures and luxations of permanent teeth. *Dental Traumatology* **28**, 2–12.

Diogenes A, Henry MA, Teixeira FB, Hargreaves KM (2013) An update on clinical regenerative endodontics. *Endodontic Topics* **28**, 2–23.

Drugs.com (2016) https://www.drugs.com/dosage/clindamycin.html#Usual_Adult_Dose_for_Bacterial_Infection. [Updated: 2016 November 1; Cited: 2016 November 28]. Available from: https://www.drugs.com/

European Society of Cardiology (2015) ESC Guidelines for the management of infective endocarditis. *European Heart Journal* **36**, 3075–123.

European Society of Endodontology Position Statement (2016) Revitalization procedures. *International Endodontic Journal* **49**, 717–23.

Farsi N, Alamoudi N, Balto K, Al Mushayt A (2006) Clinical assessment of mineral trioxide aggregate (MTA) as direct pulp capping in young permanent teeth. *Journal of Clinical Pediatric Dentistry* **31**, 72–6.

Fazakerley MW, McGowan P, Hardy P, Martin MV (1993) A comparative study of cephradine, amoxycillin and phenoxymethylpenicillin in the treatment of acute dentoalveolar infection. *British Dental Journal* **174**, 359–63.

Font-Vizcarra L, Tornero E, Bori G, Bosch J, Mensa J, Soriano A (2011) 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* **34**, 870–5.

Fouad AF, Rivera EM, Walton RE (1996) Penicillin as a supplement in resolving the localized acute apical abscess. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **81**, 590–5.

Galler KM (2016) Clinical procedures for revitalization: current knowledge and considerations. *International Endodontic Journal* **49**, 926–36.

Gomes BP, Jacinto RC, Montagner F, Sousa EL, Ferraz CC (2011) Analysis of the antimicrobial susceptibility of anaerobic bacteria isolated from endodontic infections in Brazil during a period of nine years. *Journal of Endodontics* **37**, 1058–62.

Gomes-Filho JE, Duarte PC, de Oliveira CB *et al.* (2012) Tissue reaction to a triantibiotic paste used for endodontic tissue self-regeneration of non-vital immature permanent teeth. *Journal of Endodontics* **38**, 91–4.

Gonzales R, Malone DC, Maselli JH, Sande MA (2001) Excessive antibiotic use for acute respiratory infections in the United States. *Clinical Infectious Diseases* **33**, 757–62.

Gordon D (2010) Amoxicillin–Clavulanic Acid (Co-Amoxiclav). In: Grayson ML *et al.* , eds. *Kucers' the use of antibiotics: a clinical review of antibacterial, antifungal, antiparasitic and antiviral drugs*. London: Hodder Arnold/ASM Press, pp. 193–4.

Groppo FC, Simoes RP, Ramacciato JC, Rehder V, de Andrade ED, Mattos-Filho TR (2004) Effect of sodium diclofenac on serum and tissue concentration of amoxicillin and on staphylococcal infection. *Biological and Pharmaceutical Bulletin* **27**, 52–5.

Grossman LI (1951) Polyantibiotic treatment of pulpless teeth. *Journal of American Dental Association* **43**, 265–78.

Hammarström L, Blomlöf L, Feiglin B, Andersson L, Lindskog S (1986) Replantation of teeth and antibiotic treatment. *Endodontology and Dental Traumatology* **2**, 51–7.

Hargreaves K, Cohen S (2011) *Cohen´s Pathways of the pulp*, 10th edn. St. Louis, MO: Mostby Elsevier, Ltd.

Henry M, Reader A, Beck M (2001) Effect of penicillin on postoperative endodontic pain and swelling in symptomatic necrotic teeth. *Journal of Endodontics* **27**, 117–23.

Hinckfuss SE, Messer LB (2009) An evidence-based assessment of the clinical guidelines for replanted avulsed teeth. Part II: prescription of systemic antibiotics. *Dental Traumatology* **25**, 158–64.

Hoshino E, Kurihara-Ando N, Sato I *et al.* (1996) *In vitro* antibacterial susceptibility of bacteria taken from infected root dentine to a mixture of ciprofloxacin, metronidazole and minocycline. *International Endodontic Journal* **29**, 125–30.

Jungermann GB, Burns K, Nandakumar R, Tolba M, Venezia RA, Fouad AF (2001) Antibiotic resistance in primary and persistent endodontic infections. *Journal of Endodontics* **37**, 1337–44.

Kandemir S, Ergül N (2000) Grievances in cases using antibiotics due to orodental problems and assessment of the need for antibiotics. *International Dental Journal* **50**, 73–7.

Kao FC, Hsu YC, Chen WH, Lin JN, Lo YY, Tu YK (2016) Prosthetic joint infection following invasive dental procedures and antibiotic prophylaxis in patients with hip or knee arthroplasty. *Infection Control and Hospital Epidemiology* doi: 10.1017/ice.2016.248 [Epub ahead of print].

Kaptan RF, Haznedaroglu F, Basturk FB, Kayahan MB (2013) Treatment approaches and antibiotic use for emergency dental treatment in Turkey. *Therapeutics and Clinical Risk Management* **9**, 443–9.

Keenan JV, Farman AG, Fedorowicz Z, Newton JT (2006) A Cochrane systematic review finds no evidence to support the use of antibiotics for pain relief in irreversible pulpitis. *Journal of Endodontics* **32**, 87–92.

Khemaaleelakul S, Baumgartner JC, Pruksakorn S (2002) Identification of bacteria in acute endodontic infections and their antimicrobial susceptibility. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontology* **94**, 746–55.

Kim JH, Kim Y, Shin SJ *et al.* (2010) Tooth discoloration of immature permanent incisor associated with triple antibiotic therapy: a case report. *Journal of Endodontics* **36**, 1086–91.

Kontakiotis EG, Filippatos CG, Tzanetakis GN, Agrafioti A (2015) Regenerative endodontic therapy: a data analysis of clinical protocols. *Journal of Endodontics* **41**, 146–54.

Kuriyama T, Williams DW, Yanagisawa M *et al.* (2007) Antimicrobial susceptibility of 800 anaerobic isolates from patients with dentoalveolar infection to 13 oral antibiotics. *Oral Microbiology and Immunology* **22**, 285–8.

Lacassin F, Hoen B, Leport C *et al.* (1995) Procedures associated with infective endocarditis in adults. A case control study. *European Heart Journal* **16**, 1968–74.

Lakshmanan CD (1972) The evaluation of a corticosteroid antibiotic agent in pulp capping. *Journal of the British Endodontic Society* **6**, 24–34.

LaPorte DM, Waldman BJ, Mont MA, Hungerford DS (1999) Infections associated with dental procedures in total hip arthroplasty. *Journal of Bone and Joint Surgery* **81**, 56–9.

Lee JY, Vann WF Jr, Sigurdsson A (2001) Management of avulsed permanent incisors: a decision analysis based on changing concepts. *Pediatric Dentistry* **23**, 357–60.

Lewis MAO (2008) Why we must reduce dental prescription of antibiotics: European Union Antibiotic Awareness Day. *British Dental Journal* **205**, 537–8.

Li Z, Cao L, Fan M, Xu Q (2015) Direct pulp capping with calcium hydroxide or mineral trioxide aggregate: a meta-analysis. *Journal of Endodontics* **41**, 1412–7.

Lo Schiavo A, Ruocco E, Russo T, Brancaccio G (2014) *Locus minoris resistentiae*: an old but still valid way of thinking in medicine. *Clinics in Dermatology* **32**, 553–6.

Lockhart PB, Loven B, Brennan MT, Fox PC (2007) The evidence base for the efficacy of antibiotic prophylaxis in dental practice. *Journal of the American Dental Association* **138**, 458–74.

Longman LP, Martin MV (1991) The use of antibiotics in the prevention of post-operative infection: a re-appraisal. *British Dental Journal* **170**, 257–62.

MacNeill S, Rindler E, Walker A, Brown AR, Cobb CM (1997) Effects of tetracycline hydrochloride and chlorhexidine gluconate on *Candida albicans.* An in vitro study. *Journal of Clinical Periodontology* **24**, 753–60.

Macy E (2014) Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Current Allergy and Asthma Reports* **14**, 476.

Macy E (2015) Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. *Current Opinion in Allergy and Clinical Immunology* **15**, 308–13.

Macy E, Ngor EW (2013) Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *Journal of Allergy and Clinical Immunology: In Practice* **1**, 258–63.

Mainjot A, D'Hoore W, Vanheusden A, Van Nieuwenhuysen JP (2009) Antibiotic prescribing in dental practice in Belgium. *International Endodontic Journal* **42**, 1112–7.

Martin MV, Longman LP, Hill JB, Hardy P (1997) Acute dentoalveolar infections: an investigation of the duration of antibiotic therapy. *British Dental Journal* **183**, 135–7.

Matthews D (2012) Impact of everyday oral activities on the risk of bacteraemia is unclear. *Evidence Based Dentistry* **13**, 80.

Matthews DC, Sutherland S, Basrani B (2003) Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. *Journal of the Canadian Dental Association* **69**, 660.

McWalter GM, el-Kafrawy AH, Mitchell DF (1973) Pulp capping in monkeys with a calcium-hydroxide compound, an antibiotic, and a polycarboxylate cement. *Oral Surgery, Oral Medicine, Oral Pathology* **36**, 90–100.

Miller EK, Lee JY, Tawil PZ, Teixeira FB, Vann WF Jr (2012) Emerging therapies for the management of traumatized immature permanent incisors. *Pediatric Dentistry* **34**, 66–9.

Miyashita H, Worthington HV, Qualtrough A, Plasschaert A (2007) Pulp management for caries in adults: maintaining pulp vitality. *Cochrane Database of Systematic Reviews* (**2**) Art. No.: CD004484. doi: 10.1002/14651858.CD004484.pub2

Mjör IA, Ostby BN (1966) Experimental investigations on the effect of Ledermix on normal pulps. *Journal of Oral and Therapeutic Pharmacology* **2**, 367–75.

Mohammadi Z (2009) Systemic, prophylactic and local applications of antimicrobials in endodontics: an update review. *International Dental Journal* **59**, 175–86.

Mohammadi Z, Abbott PV (2009) Antimicrobial substantivity of root canal irrigants and medicament: a review. *Australian Endodontic Journal* **35**, 131–39.

Molander A, Reit C, Dahlén G (1990) Microbiological evaluation of clindamycin as a root canal dressing in teeth with apical periodontitis. *International Endodontic Journal* **23**, 113–8.

Montefusco V, Gay F, Spina F *et al.* (2008) 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* **49**, 2156–62.

Moore PA (1999) Dental therapeutic indications for the newer long-acting macrolide antibiotics. *Journal of the American Dental Association* **130**, 1341–3.

Murdoch DA (1998) Gram-positive anaerobic cocci. *Clinical Microbiology Reviews* **11**, 81–120.

Murray PE, Garcia-Godoy F, Hargreaves KM (2007) Regenerative endodontics: a review of current status and a call for action. *Journal of Endodontics* **33**, 377–90.

Nagle D, Reader A, Beck M, Weaver J (2000) Effect of systemic penicillin on pain in untreated irreversible pulpitis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **90**, 636–40.

NICE (2008) Prophylaxis against infective endocarditis. http://nice.org.uk/.

NIDCR (2009) Oral Complications of Cancer Treatment: What the Oral Health Team Can Do. September 2009. Available at: http://www.nohic.nidcr.nih.gov/campaign/den_fact.htm. Accessed on November the 18, 2016.

Nishimura RA, Carabello BA, Faxon DP, Freed MD, Lytle BW *et al.* (2008) ACC/AHA 2008 guideline update on valvular heart disease: focused update on infective endocarditis: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* **118**, 887–96.

Olsen I, Snorrason F, Lingaas E (2010) Should patients with hip joint prosthesis receive antibiotic prophylaxis before dental treatment? *Journal of Oral Microbiology* **2**, 5265.

Pallasch TJ (1993) How to use antibiotics effectively. *Journal of the California Dental Association* **21**, 46–50.

Pallasch TJ (2000) Global antibiotic resistance and its impact on the dental community. *Journal of the California Dental Association* **28**, 215–33.

Palmer NA, Pealing R, Ireland RS, Martin MV (2000) A study of therapeutic antibiotic prescribing in National Health Service general dental practice in England. *British Dental Journal* **188**, 554–8.

Paryani K, Kim SG (2013) Regenerative endodontic treatment of permanent teeth after completion of root development: a report of 2 cases. *Journal of Endodontics* **39**, 929–34.

Peric M, Perkovic I, Romic M *et al.* (2015) The pattern of antibiotic prescribing by dental practitioners in Zagreb, Croatia. *Central European Journal of Public Health* **23**, 107–13.

Poveda Roda R, Bagán JV, Sanchis Bielsa JM, Carbonell Pastor E (2007) Antibiotic use in dental practice. A review. *Medicina Oral, Patología Oral y Cirugía Bucal* **12**, E186–92.

Richey R, Wray D, Stokes T (2008) Prophylaxis against infective endocarditis: summary of NICE guidance. *British Medical Journal* **336**, 770–1.

Roche Y, Yoshimori RN (1997) *In vitro* activity of spiramycin and metronidazole alone or in combination against clinical isolates from odontogenic abscesses. *Journal of Antimicrobial Chemotherapy* **40**, 353–77.

Rodríguez-Benítez S, Stambolsky C, Torres-Lagares D, Gutiérrez-Pérez JL, Segura-Egea JJ (2015) Pulp revascularization of immature dog teeth with apical periodontitis using tri-antibiotic paste and platelet-rich plasma: radiographic study. *Journal of Endodontics* **41**, 1299–304.

Rodriguez-Núñez A, Cisneros-Cabello R, Velasco-Ortega E, Llamas-Carreras JM, Tórres-Lagares D, Segura-Egea JJ (2009) Antibiotic use by members of the Spanish Endodontic Society. *Journal of Endodontics* **35**, 1198–203.

Sato I, Ando-Kurihara N, Kota K *et al.* (1996) Sterilization of infected root-canal dentine by topical application of a mixture of ciprofloxacin, metronidazole and minocycline *in situ*. *International Endodontic Journal* **29**, 118–24.

Schwartzberg LS (2006) Neutropenia: etiology and pathogenesis. *Clinical Cornerstone* **8**(Suppl. 5), S5–11.

Segura-Egea JJ, Velasco-Ortega E, Torres-Lagares D, Velasco-Ponferrada MC, Monsalve-Guil L, LLamas-Carreras JM (2010) Pattern of antibiotic prescription in the management of endodontic infections among Spanish oral surgeons. *International Endodontic Journal* **43**, 342–50.

Seymour RA, Whitworth JM, Martin M (2003) Antibiotic prophylaxis for patients with joint prostheses - still a dilemma for dental practitioners. *British Dental Journal* **194**, 649–53.

Siqueira JF, Roças I (2014) Present status and future directions in endodontic microbiology. *Endodontic Topics* **30**, 3–22.

Skučaitė N, Pečiulienė V, Manelienė R, Mačiulskienė V (2010) Antibiotic prescription for the treatment of endodontic pathology: a survey among Lithuanian dentists. *Medicina* **46**, 806–13.

Slots J (2002) Selection of antimicrobial agents in periodontal therapy. *Journal of Periodontal Research* **37**, 389–98.

Soldati GD (1974) Pulp capping with antibiotics. *New York Journal of Dentistry* **44**, 120–2.

Stein GE, Schooley S, Tyrrell KL, Citron DM, Goldstein EJ (2007) Human serum activity of telithromycin, azithromycin and amoxicillin/clavulanate against common aerobic and anaerobic respiratory pathogens. *International Journal of Antimicrobial Agents* **29**, 39–43.

Strom BL, Abrutyn E, Berlin JA *et al.* (1998) Dental and cardiac risk factors for infective endocarditis. A population-based, case-control study. *Annals of Internal Medicine* **129**, 761–9.

Takushige T, Cruz EV, Asgor Moral A, Hoshino E (2004) Endodontic treatment of primary teeth using a combination of antibacterial drugs. *International Endodontic Journal* **37**, 132–8.

Tang G, Samaranayake LP, Yip HK (2004) Molecular evaluation of residual endodontic microorganisms after instrumentation, irrigation and medication with either calcium hydroxide or Septomixine. *Oral Diseases* **10**, 389–97.

Thibodeau B, Trope M (2007) Pulp revascularization of a necrotic infected immature permanent tooth: case report and review of the literature. *Pediatric Dentistry* **29**, 47–50.

Thornhill MH, Dayer M, Lockhart PB *et al.* (2016) A change in the NICE guidelines on antibiotic prophylaxis. *British Dental Journal* **221**, 112–4.

Tolentino Ede S, Centurion BS, Ferreira LH, Souza AP, Damante JH, Rubira-Bullen IR (2011) 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* **19**, 448–54.

Torabinejad M, Khademi AA, Babagoli J *et al.* (2003) A new solution for the removal of the smear layer. *Journal of Endodontics* **29**, 170–5.

Tulip DE, Palmer NO (2008) A retrospective investigation of the clinical management of patients attending an out of hours dental clinic in Merseyside under the new NHS dental contract. *British Dental Journal* **205**, 659–64.

Uckay I, Pittet D, Bernard L, Lew D, Perrier A, Peter R (2008) Antibiotic prophylaxis before invasive dental procedures in patients with arthroplasties of the hip and knee. *Journal of Bone and Joint Surgery* **90**, 833–8.

U.S. National Library of Medicine, Daily Med: Current Medication Information (2006) "Penicillin V Potassium tablet: Drug Label Sections". Retrieved 2016-11-28. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3111ca84-6f8e-45ea-91a1-9cb99c63607e.

Waldman BJ, Mont MA, Hungerford DS (1997) Total knee arthroplasty infections associated with dental procedures. *Clinical Orthopaedics and Related Research* **343**, 164–72.

Warnke PH, Becker ST, Springer IN *et al.* (2008) Penicillin compared with other advanced broad spectrum antibiotics regarding antibacterial activity against oral pathogens isolated from odontogenic abscesses. *Journal of Cranio-maxillofacial Surgery* **36**, 462–7.

Wigler R, Kaufman AY, Lin S, Steinbock N, Hazan-Molina H, Torneck CD (2013) Revascularization: a treatment for permanent teeth with necrotic pulp and incomplete root development. *Journal of Endodontics* **39**, 319–26.

Wilson W, Taubert KA, Gewitz M *et al.* (2007) Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Journal of the American Dental Association* **138**, 739–60.

Yoshiba K, Yoshiba N, Iwaku M (1995) Effects of antibacterial capping agents on dental pulps of monkeys mechanically exposed to oral microflora. *Journal of Endodontics* **21**, 16–20.

Zeitoun IM, Dhanarajani PJ (1995) Cervical cellulitis and mediastinitis caused by odontogenic infections: report of two cases and review of literature. *Journal of Oral Maxillofacial Surgery* **53**, 203–8.