1.3

Management of Odontogenic Infections: Indications for Antibiotics

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Introduction

One in four children has their first encounter with a dentist due to an emergency situation (Agostini et al., 2001). Depending on the child's age and the appointment setting (e.g. hospital or dental clinic), the emergency may be related to pain (82%), dental caries (40–79%), soft-tissue disease (4–20%), disease of the pulp and periapical tissue (40%), dental trauma (6–51%) or cellulitis and abscess of the mouth (3%) (Rowley et al., 2006; Shqair et al., 2012; Allareddy et al., 2014). Many of these conditions are caused by an odontogenic infection, which may require antibiotic therapy in order to control infection and prevent bacterial spread. However, as childhood is a period of continuous growth and development, administration of antibiotics in children should be carefully evaluated. Long-term administration may cause peculiar neurologic and physical abnormalities such as neurodevelopmental dysfunction, enamel hypo- and dysplasia, discoloration of teeth and dysfunction in bone growth (Reed and Besunder, 1989; Alcorn and McNamara, 2003; Sánchez et al., 2004). Further, dosages in paediatric patients must be adjusted for their lower weight and body size (Agarwal et al., 2014). Dentists have raised questions about the risks and benefits of antibiotic administration for prophylactic or therapeutic purposes due to the development of resistant microbial strains, doubts over the efficacy of prophylactic regiments, possible adverse reactions and poor compliance by patients (Agarwal et al., 2014).

The scientific literature includes a number of guidelines on whether to administer antibiotics (Palmer, 2006; Agarwal et al., 2014; Caviglia et al., 2014; AAPD, 2016a,b,c). One of the best-accepted is that from the American Academy of Pediatric Dentistry (AAPD, 2016a,b,c). However, studies reveal a low adherence to these guidelines, varying between 6 and 33% (Coutinho et al., 2009; Cherry et al., 2012; Yesudian et al., 2015). A recent study showed that dentists are overprescribing antibiotics for children, and that at least 21% of the dosages recommended for children were inappropriate (Michael and Hibbert, 2014). Fortunately, dentists are aware that antibiotic resistance is a growing problem (Sivaraman et al., 2013). Studies have shown that following educational measures, the percentage of appropriate recommendations can increase (Palmer et al., 2001; Palmer and Dailey, 2002; Yesudian et al., 2015). Therefore, the aim of this chapter is to summarise the current literature in order to assist clinicians in their decision-making process.

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Antibiotic Resistance, Misuse and Adverse Drug Events

Dental professionals are responsible for 10% (almost 25 million) of all antibiotic prescriptions worldwide (Hicks et al., 2015; CDC, 2017). Thus, they must be responsible in their recommendations, in order to minimise the risk of adverse events and reduce the spread of antibiotic-resistant bacteria (Fluent et al., 2016). According to the literature, six events can occur when antibiotics are applied (Pallasch, 2000):

1) The antibiotic may aid the immune system to gain control of the infection.
2) Toxicity or allergy may occur.
3) Already resistant microbes may be selected for, and a superinfection may result.
4) The antimicrobial may promote microbial chromosomal mutations.
5) Gene transfer from resistant to nonresistant microbes may be encouraged.
6) Latent resistance genes may be expressed.

Antibiotic Resistance

Antibiotic resistance is a major global health threat. Every year in the United States alone, at least 2 million people became infected with antibiotic-resistant bacteria, and about 23 000 die as a direct result of these infections (CDC, 2017). A study performed in adults with isolated microorganisms from orofacial infections found significant rates of antibiotic-resistant bacteria: 32.5% showed resistance to penicillin, 29.3% to clindamycin and 30% to erythromycin (Kim et al., 2017). Clinicians and patients play a fundamental role in the development of antibiotic resistance. Clinicians should avoid overprescription, whilst patients should be aware that antibiotics should not be applied for every type of pain or problem. According to Pallasch (2000), the main reasons for the inappropriate use of antibiotics are:

- Insufficient training in infectious diseases and proper antibiotics therapy.
- Empirical use.
- Lack of culture and sensitivity tests.
- Inadequate diagnosis.
- Inappropriate choice of drug, dose and duration.
- Need for self-assurance.
- Patient demand.
- Fear of litigation.

Antibiotic resistance may be prevented through a few strategies aimed at minimising the emergence of resistant bacteria (AAPD, 2016b; CDC, 2017), including improving clinician training and providing patients with information on antibiotic therapy (Palmer et al., 2001; Palmer and Dailey, 2002; Jain et al., 2015; Yesudian et al., 2015; CDC, 2017). Patient compliance is a key factor in order in reducing the emergence of resistant bacteria. Patients should be aware of when antibiotics will and won't help. They should only take antibiotics exactly as prescribed, and shouldn't save them for later or share them with others (CDC, 2017).

In summary, the most important aspect in minimising the emergence of antibiotic resistance is improving prescription of antibiotics by means of the education of clinicians and patients. The key is to prescribe the right antibiotic, at the right dosage and drug interval, for the right time period and at the right time point, according to well-accepted guidelines. The development of antibiotic resistance can thus be reduced.

Misuse of Antibiotics in Dentistry

The key to avoiding misuse of antibiotics in dentistry is to correctly diagnose patient complaints. A detailed medical and dental history, an extraoral/intraoral clinical examination and a radiographic analysis are necessary for an adequate diagnosis, and the subsequent provision of a treatment plan (with or without the use of antibiotic medication). The misuse of antibiotic drugs in dentistry involves their application in inappropriate clinical situations, their administration for too short or too long a period of time and further situations such as

(Pallasch, 2000; Palmer, 2006; Michael and Hibbert, 2014):

- Giving antibiotics after a dental procedure is completed in an otherwise healthy patient in order to "prevent" an infection (that is, to prevent a lawsuit, in many cases), which in all likelihood will not occur.
- Using antibiotics as "analgesic."
- Employing antibiotics for prophylaxis in a patient not at risk for metastatic bacteraemia.
- Using antimicrobials to treat chronic adult periodontitis.
- Using antimicrobial therapy in lieu of mechanical therapy in periodontitis management.
- Using antibiotics instead of surgical incision and drainage of infections.
- Using antibiotic to "prevent" claims of negligence.

Adverse Drug Events

Adverse drugs events (ADEs) are the most common cause of iatrogenic harm in health care and have recently received attention in national patient safety initiatives (Shehab et al., 2016). Amongst children, ADEs related to antibiotics are the most frequent cause of emergency department visits (CDC, 2017): 27.5% of ADEs affect children aged 0–18 years (Bourgeois et al., 2009). In a study based on more than 42 500 ADE cases, it was found that 46.4% were related to antibiotics at age 5 years and younger, and 31.8% at ages 6–19 (Shehab et al., 2016). The most commons ADEs include dermatologic, gastrointestinal, neurological, psychological, endocrine, respiratory and cardiovascular symptoms, general malaise/fever, oedema/swelling and sensory or motor disturbance (syncope/dizziness/muscular weakness) (Bourgeois et al., 2009; Shehab et al., 2016).

Patients should be aware that the following ADEs may occur during antibiotic therapy: rash, diarrhoea (including Pseudomembranous colitis or *Clostridium difficile* infection), abdominal pain, gastrointestinal disturbance, nausea/vomiting, drug fever, joint pain, weakness, taste alterations, tooth discoloration in children <8 years, jaundice, dizziness, drowsiness, headache, insomnia, metallic mouth taste and hypersensitivity reactions (Table 1.3.1). In the drug class of penicillins – the first choice of antibiotic for dental treatment – hypersensitivity is one of the most frequent ADEs. Reactions can range from a simple rash or urticaria in 1–7% of cases (Palmer, 2006) to a life-threatening, severe anaphylactic reaction in 0.004–0.2% (Caviglia et al., 2014).

Indications for Antibiotic Therapy

Indications for Using Antibiotic Therapy

Antibiotics should always be applied in addition to causative dental treatment and should never be used as the exclusive therapy of choice. Antibiotics cannot serve as a substitute for surgical or endodontic treatment, for the following reasons (Pallasch, 1993, 1996, 2000): antibiotics do not diffuse well into infected areas; blood supply to abscesses is usually compromised; due to the acidic environment and low pH level within dentoalveolar infections, some antibiotics are ineffective; high levels of antibiotic inhibitors (beta-lactamases) may be present in infections; and the efficacy of penicillins and cephalosporins is reduced in infections where microorganisms are dividing slowly or not at all.

The use of antibiotics in dentistry is indicated for two major reasons: to control oral infection and to prevent bacteraemia precipitated by dental manipulations from causing severe systemic sequelae (Agarwal et al., 2014). In general, consideration should be given to the patient's systemic condition, the patient's symptoms, the intraoral localisation, the extension of the inflammation, the type of wound and the progression of the disease. In 2016, the AAPD revised its guidelines concerning indications for antibiotic therapy in paediatric dental patients with the

Table 1.3.1 The main antibiotics used in paediatric dental patients (according to Palmer, 2006; Agarwal et al., 2014; Caviglia et al., 2014; and Donaldson et al., 2015).

Name	Oral dosage – drug interval			Side effects (most common)	Additional information
	Agarwal et al. (2014)	Caviglia et al. (2014)	Donaldson et al. (2015)		
Amoxicillin	50–90 mg/kg/day 08–12 h	20–50 mg/kg/day 08 h	20–90 mg/kg/day 08–12 h	Nausea/vomiting, abdominal pain, diarrhoea, drug fever, hypersensitivity reaction	First choice in dentistry – broad-spectrum penicillin
Amoxicillin–Clavulanate potassium	45–50 mg/kg/day 08 h	40–80 mg/kg/day 08 h	25–90 mg/kg/day 12 h	Nausea/vomiting, abdominal pain, diarrhoea, drug fever, hypersensitivity reaction	Indicated in cases of late untreated infection or bad evolution after treatment with first choice
Ampicilin	50–100 mg/kg 06 h	–	–	Nausea/vomiting, abdominal pain, diarrhoea, drug fever, hypersensitivity reaction, fever, headache, weakness	Preferred to be administered parenterally
Azithromycin	–	–	5–10 mg/day Once day × 4 days	Nausea/vomiting, abdominal pain, diarrhoea, dizziness, taste alterations	Alternative to amoxicillin, similar to erytromycin
Clarithromycin	–	7.5–15 mg/kg/day 12 h	7.5 mg/kg 12 h	Nausea/vomiting, abdominal pain, headache, insomnia, taste alterations	Useful for patient allergic to penicillin – good soft-tissue diffusion
Clindamycin	–	10–30 mg/kg/day 06 h	10 mg/kg 08 h	Nausea/vomiting, abdominal pain, diarrhoea (pseudomembranous colitis), joint pain, jaundice	Useful for patients allergic to penicillin – good bone-tissue diffusion
Doxycycline[a]	–	–	2–4 mg/kg/day 12 h	Nausea/vomiting, abdominal pain, diarrhoea, discoloration of permanent teeth	–
Erytromycin	30–50 mg/kg 06 h	–	7.5–12.5 mg/kg 06 h	Nausea/vomiting, abdominal pain, diarrhoea, dizziness	Useful for patient allergic to penicillin
Metronidazole	30–50 mg/kg 06 h	–	30 mg/kg/day 06 h	Nausea/vomiting, taste alterations, gastrointestinal disturbances, drowsiness, dizziness, headache	Usually indicated in periodontal diseases, in association with penicillin
Penicillin	25–50 mg/kg 06–12 h	–	25–50 mg/kg/day 06–08 h	Nausea/vomiting, abdominal pain, diarrhoea, drug fever, hypersensitivity reaction	Alternative to amoxicillin
Tetracycline[a]	–	–	25–50 mg/kg/day 06 h	Nausea/vomiting, diarrhoea, discoloration of permanent teeth, swollen tongue	First systemic choice in cases of avulsion of permanent teeth Alternative in cases of treatment of AP

[a] Not recommended for children younger than 8 years, because this is the period in which tooth enamel is being formed (Shetty, 2002).
AP, agressive periodontitis.

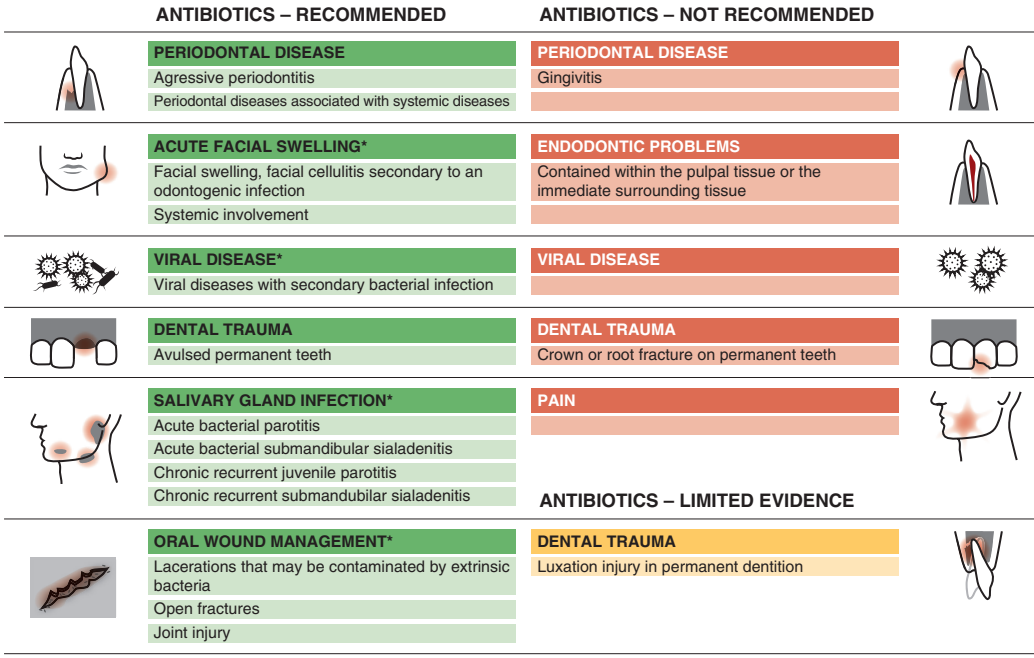

Figure 1.3.1 Clinical situations in which antibiotic therapy is and is not indicated for paediatric dental patients.

following recommendations (AAPD, 2016b) (Figure 1.3.1):

A) **Oral wound management**
- Facial lacerations may require topical antibiotic agents.
- Intraoral lacerations that may be contaminated by extrinsic bacteria, open fractures and joint injury should be covered with antibiotics.

B) **Pulpitis/apical periodontitis/draining sinus tract/localised intraoral swelling**
- Antibiotic therapy usually is not indicated if the dental infection is contained within the pulpal tissue or the immediate surrounding tissue.
- Antibiotics may be an option for cases of advanced nonodontogenic bacterial infection such as staphylococcal mucositis, tuberculosis, gonococcal stomatitis and oral syphilis.

C) **Acute facial swelling of dental origin**
- Children with facial swelling, facial cellulitis secondary to an odontogenic infection and any signs of systemic involvement should receive immediate dental attention.

D) **Dental trauma**
- Antibiotics are recommended for avulsed permanent incisors with open or closed apex.
- Antibiotics are generally not indicated for cases of luxation involving the primary dentition.

E) **Pediatric periodontal diseases**
- Cases of periodontal diseases associated with systemic diseases (e.g. severe congenital neutropenia, Papillon–Lefèvre syndrome, leukocyte adhesion deficiency) may require adjunctive antibiotic therapy.

F) **Viral diseases**
- Conditions of viral origin should not be treated with antibiotics unless there is strong evidence that a secondary bacterial infection exists.

G) **Salivary gland infection**
- If there is confirmation of bacterial aetiology, some salivary gland infection

and acute bacterial parotitis and chronic recurrent juvenile parotitis, antibiotic therapy is recommended.
- In cases of acute bacterial submandibular sialadenitis and chronic recurrent submandibular sialadenitis, the use of antibiotics is already included as part of the treatment.

Complementing the topic of dental trauma, the International Association of Dental Traumatology (IADT) provides a series of guidelines for the management of traumatic dental injuries (TDIs) in the primary and permanent dentition (Andersson et al., 2012, 2016; DiAngelis et al., 2012, 2016; Malmgren et al., 2012, 2016). Together with one literature review (Andreasen et al., 2006), their conclusions about the use of antibiotics are as follows (Figure 1.3.1):

1) **Fractures and luxations of permanent teeth:** There is limited evidence for the use of systemic antibiotics in the management of luxation injury and no evidence for root-fracture teeth.
2) **Avulsion of permanent teeth:** Antibiotics are in most situations recommended after replantations of teeth (with closed or open apex). Positive effects (periodontal and pulpal healing) are observed when antibiotics are prescribed, both systemically and topically.
3) **Injuries in the primary dentition:** There is no evidence for the use of systemic antibiotics in the management of luxation injuries in the primary dentition.

In the area of periodontology, young children and adolescents may be affected by necrotising ulcerative gingivitis (NUG). If this condition is accompanied by fever, malaise or lymphadenopathy, antibiotic therapy is indicated (Agarwal et al., 2014; AAPD, 2016c). Aggressive periodontitis (AP), chronic periodontitis (CP) and periodontitis as a manifestation of systemic disease can also affect children and adolescents. During treatment of AP and periodontitis as a manifestation of systemic disease, the use of antibiotics is usually beneficial (AAPD, 2016c) (Figure 1.3.1).

The clinician should always consider whether the patient can be treated in the dental practice or should be referred to a hospital setting. Referral should always be considered in cases presenting signs of septicaemia (grossly elevated temperature, lethargy, tachycardia), spreading cellulitis, swelling compromising the airway (causing closure of the eye or difficulty in swallowing), dehydration or failure to respond to treatment, as well as with uncooperative patients (Palmer, 2006).

Indications for Not Using Antibiotic Therapy

According to the literature, antibiotic therapy should not be administered for dental treatment under the following conditions: management of dental pain, localised swelling or dental infections contained within the pulpal tissue or the immediate surrounding tissue, gingivitis and management of viral infections without secondary bacterial infections (Palmer, 2006; Agarwal et al., 2014; AAPD, 2016b). A systematic review of the literature (Matthews et al., 2003) concluded that the use of antibiotics in the management of localised dental infections is not recommended as a substitute for causative dental treatment. In addition, the effectiveness of oral antibiotics as a sole treatment for an odontogenic infection is highly questionable, due to the lack of effective circulation in a necrotic pulp or an abscess (Swift and Guiden, 2002) (Figure 1.3.1).

Time Point, Time Period, Dosage and Drug Interval of Antibiotic Therapy

Time Point and Time Period

There is a consensus that antibiotics should be administered as soon as possible for optimal results. They should continue to be applied for a minimum of 5 days beyond the point of substantial improvement of symptoms

(Agarwal et al., 2014; AAPD, 2016b). This may represent a total of 5–7 days of treatment, depending upon the specific drug selected. However, the clinician must always monitor the clinical effectiveness of the therapy. In cases of ineffectiveness before the course is completed, alteration or discontinuation should be considered (AAPD, 2016b). In addition, a lack of patient compliance should be taken into account as a potential reason for a limited response.

Dosage and Drug Interval

Two types of error in the dosage of antibiotics should be considered: underdosage and overdosage. Underdosage may produce an inadequate concentration of the drug at the infected site, fostering recurrent infections and development of resistant bacterial strains. Overdosage, on the other hand, may result in damage to the host's response, producing toxic effects and increasing the risk of ADEs (Swift and Guiden, 2002). The dosages, drug intervals and most common side effects of the main antibiotics are listed in Table 1.3.1.

Antibiotic Prophylaxis

Antibiotic prophylaxis (AP) is used in order to prevent a bacteraemia caused by dental manipulations leading to severe systemic sequelae prior to invasive dental procedures. It is recommended for patients at high risk of developing infective endocarditis (IE) and for those affected by several immunocompromised conditions (Donaldson et al., 2015) (Table 1.3.2).

Infective Endocarditis

IE is a microbial infection of intracardiac structures. It often occurs on previously damaged or congenitally malformed cardiac valves or endocardium. It is an uncommon but serious and life-threatening disease (Wilson et al., 2007; Murdoch et al., 2009; Glenny et al., 2013). There is a controversy concerning the real efficacy and safety of AP in preventing IE in dentistry, due to a lack of prospective, randomised, placebo-controlled clinical trials to support evidence-based decisions (Glenny et al., 2013; Lockhart et al.,

Table 1.3.2 American Heart Association (AHA) antibiotic prophylaxis (AP) regimens for a dental procedure. (Wilson et al., 2007. Reprinted with permission. © 2007, American Heart Association, Inc.)

Situation	Agent	Single dose 30–60 minutes before procedure
		Children
Oral	Amoxicillin	50 mg/kg
Unable to take oral medication	Ampicillin OR cefazolin or ceftriaxone	50 mg/kg IM or IV
Allergic to penicillins or ampicillin – oral	Cephalexin[a,b] OR	50 mg/kg
	Clindamycin OR	20 mg/kg
	azithromycin or clarithromycin	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[b] OR	50 mg/kg IM or IV
	Clindamycin	20 mg/kg IM or IV

[a] Or other first- or second-generation oral cephalosporin in equivalent paediatric dosage.
[b] Cephalosporin should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin.
IM, intramuscular; IV, intravenous.

2013; Baltimore et al., 2015; Donaldson et al., 2015; Cahill et al., 2017). In addition, the frequency of bacteraemia appears to be greater in daily oral hygiene and nutrition by patients, rather than cases resulting from dental procedures such as tooth extraction, periodontal surgery and others. Therefore, several IE episodes can be prevented by maintenance of good oral hygiene and access to a regular maintenance care programme (Wilson et al., 2007; Baltimore et al., 2015; Habib et al., 2015; NICE, 2015; AAPD, 2016a). The antibiotic regimens recommended by the American Heart Association (AHA) for AP are listed in Table 1.3.2.

According to the AHA and the European Society of Cardiology (ESC), AP is recommended for patients in the highest risk group before being submitted to high-risk dental procedures:

- Highest-risk patients exhibit cardiac conditions such as: cardiac valve repair with prosthetic cardiac valve or prosthetic material; previous IE; cardiac valvulopathy in a cardiac transplantation recipient; and congenital heart disease (CHD) – unrepaired cyanotic CHD (including palliative shunts and conducts), completely repaired CHD with prosthetic material or a prosthetic device (whether placed by surgery or catheter intervention during the first 6 months after the procedure), and repaired CHD with residual defects at or adjacent to the site of a prosthetic patch or prosthetic device (Wilson et al., 2007; Habib et al., 2015).
- High-risk dental procedures involve manipulation of gingival (including extractions and scaling) or periapical (including root canal) regions of the teeth or perforation of the oral mucosa. Minor procedures such as routine anaesthetic injections through noninflected tissue, treatment of superficial caries not requiring gingival manipulation, removal of sutures, taking of dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa do not require AP (Wilson et al., 2007; Habib et al., 2015; Thornhill et al., 2016).

Regarding the controversy over AP in dental patients, the literature contains three main guidelines on prevention of IE. The AHA (Wilson et al., 2007) and ESC (Habib et al., 2015) guidelines are almost the same, recommending AP for the highest-risk patients when performing high-risk procedures, but the British guidelines (National Institute for Health and Care Excellence, NICE) do not recommend AP for any type of patient or procedure (NICE, 2015). Two recent publications, one from the AAPD (2016a) and one from the AHA (Baltimore et al., 2015), together with a systematic review with meta-analyses (Cahill et al., 2017), recommend that patients considered as high-risk should receive AP when submitted to high-risk procedures.

Clinician adherence to these guidelines is low. Research suggests that this may be because the clinicians disagree with them, or it may be that the guidelines are too vague or too difficult to remember (Jain et al., 2015). Coutinho et al. (2009), in a preliminary study, showed that only 33% of subjects interviewed said they followed the AHA guidelines. Lockhart et al. (2013) found that 70% of dentists still recommended AP for patients not considered at high risk for developing IE.

Immunocompromised Patients

Immunocompromised patients suffer from one or more defects of the immune system, exhibiting an increased risk of infection. These patients may develop a primary or secondary/acquired immunodeficiency such as cancer, need for an organ transplant, poorly controlled diabetes, HIV infection and neutrophil disorders (Fleming and Palmer, 2006; Donaldson et al., 2015). In immunocompromised patients, oral infection should be avoided. Therefore, a regular maintenance care programme, including ongoing preventative dental care, is key for these patients (Fleming and Palmer, 2006). In most cases where dental treatment is necessary, the clinician should consider working in very close collaboration with physicians or the

medical team in order to decide on the best strategy for the individual case (Donaldson et al., 2015). Due to its immunosuppressive qualities, the use of AP prior to an invasive dental procedure is suggested in these patients. According to Donaldson et al. (2015), AP for immunocompromised patients should follow the same antibiotic regimens as recommended for IE (Table 1.3.2).

Conclusion

Key to the administration of an antibiotic regimen is prescribing the right antibiotic, at the right dosage and drug interval, for the right time period and at the right time point according to well-accepted guidelines. When facing a clinical situation, the clinician should find the aetiology of the patient complaint based on their medical and dental history, extra/intraoral examination and radiographic analysis, in order to reach the appropriate diagnosis. Following diagnosis, the clinician should choose an appropriate treatment plan. Several modalities can be included, such as endodontic therapy, surgical/mechanical disruption of the infectious environment and replantation of avulsed teeth. Associated with the treatment plan, and according to the guidelines presented in the literature, supportive antibiotic therapy or AP may be indicated. The clinician should monitor the patient to ensure the efficacy of the treatment. In case of persistent symptoms, the treatment plan should be revised and modified where necessary. For paediatric dental patients with any type of systemic disease, a team approach involving the clinician and the physician is important in conducting and resolving the case.

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