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Clinical practice guideline for pharmacological management of pain and swelling in endodontic emergencies

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***Abstract*---**Endodontic pain is one of the most predominantly associated symptoms. The pain may arise due to either because of an endodontic cause (or) a periradicular cause, importantly endodontic pain type variant is the most commonly encountered by the dentist in their clinical practice. The objective of endodontic treatment is to prevent or cure apical periodontitis (AP) caused by infection of the root canal systems of the affected teeth (or) due to persistence of primary infection (or) emergence of infection after treatment [1]. An online search was conducted in MEDLINE, Embase, the Cochrane library and the cumulative Index to Nursing and Allied Health literature to retrieve evidence on benefits and harm associated with antibiotic use & review articles by utilizing the following keywords: Antibiotics, symptomatic Irreversible pulpitis, symptomatic apical periodontitis, pulp necrosis, localized acute apical abscess, clinical practice guidelines. The clinician must systematically gather all of the necessary information to make a "probable diagnosis" Endodontic diagnosis is similar to a Jigsaw puzzle diagnosis cannot be made from a single isolated piece of information. The indications are based on the clinical diagnosis of Normal pulp, reversible pulpitis, symptomatic (or) asymptomatic Irreversible pulpitis & necrotic pulp (or) localized acute apical abscess [2].Clinical guidelines for pharmacological management of pain & swelling in endodontic emergencies have not been formulated. Decision on management should consider the following: Clinical recommendations for the urgent management of symptomatic irreversible pulpitis with or without symptomatic apical periodontitis, pulp necrosis and localized acute apical abscess. Clarifying the stages of antibiotic usage during emergency management .Evaluate the

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status of antibiotics usage, during emergency management. Clinical experience and understanding of these influencing factors as well as the ability to make a balanced decision are essential.

***Keywords*---**clinical practice guidelines, antibiotics, symptomatic irreversible pulpitis, symptomatic apical periodontitis, pulp necrosis.

Introduction

The spectrum of endodontic pathosis includes many conditions for which dentist and endodontist determine that it is appropriate to prescribe antibiotics. Some of these conditions involve purely an inflammatory reaction, and some involve various stages of infection. This infection may be localized to the pulp and periapical tissues, and it may be spreading systemically. Because of polymicrobial nature, endodontic infection is complex consisting of gram positive, gram negative and facultative anaerobes. The causative microorganism causing endodontic infection cannot be identified and most commonly broad spectrum antibiotics are prescribed. Irrational and overuse of antibiotics results in the emergence of antibiotic resistance and also increases the risk of hypersensitivity reactions, like anaphylaxis. The purpose of this guidelines is too concise and provide an evidence based knowledge on antibiotic prescription and their usage in endodontic.

The endodontic pain is mainly caused due to the inflammation of the pulp tissue occurring as a result of dental caries progressing deep into the tooth. This pain arises in response to either reversible or Irreversible pulpitis. The reversible pulpitis can be characterized by acute pain unlike the steady chronic pain in case of Irreversible pulpitis. The acute pain is what brings the patient to a dental clinic due to its intolerable nature and so the precise diagnosis and systematic treatment would only relieve pain from the patient. The causes of endodontic pain contains of a broad spectrum which needs to analysed properly before arriving at a diagnosis.

Most of the endodontic infections are well controlled by debridement of the root canal through cleaning and shaping procedures. The use of systematic antibiotics as adjuncts is justified only in cases of acute apical abscess with systematic involvement like malaise, elevated body temperature and lymphadenopathy, progressing infections like cellulitis & osteomyelitis[3]. Acute apical periodontitis (AAP) is due to necrosis of pulp, recommended treatment is to remove the necrotic pulp tissue which done via access through the tooth and extirpation of necrotic pulp[4]. Further, other various therapies used on their own or in conjunction with pulpectomy to relieve patient's symptoms, which include use of systemic or local medicaments, such as corticosteroids, analgesics and antibiotics. However the pain of AAP is not a result of an infectious process, thus, the use of antibiotics as a therapy may be questionable. Despite this, up to 75% patients with painful AAP are treated with antibiotic therapy[5, 6].

Attributing success or failure to a particular clinical technique (or) procedure is often problematic. It is not unusual for clinicians to review cases seemingly

similar in nature that respond differently to the same clinical approach. This article will review procedures used to treat endodontic emergencies in the context of relevant controlled clinical trials and their underlying biological principles. This document is intended to present the available evidence related to prescribing antibiotics, highlight appropriate clinical recommendations and identify gaps in knowledge for which personal judgement is the best guide for assessing risks and benefits in this practice.

Status of Antibiotics usage, during emergency management

The therapeutic use of antibiotics relies on achieving at least the minimal inhibitory concentration (MIC) of the drug, against sensitive microorganisms at the site of infection. In the case of advanced endodontic infections, the dental pulp tissue after succumbing to liquefaction necrosis is no longer vascularized, and orally administered drugs are unable to reach the site of infection. Therefore, the drug distribution is restricted to the surrounding vascularized tissues. However, in cases of apical abscess, the presence of pus limits vascular supply, and contains cellular debris and proteins that can bind and sequester antibiotics making these drugs less effective in the absence of adequate drainage[7].

Thus, antibiotics should only be used as adjuvant therapies in cases with evidence of systemic involvement (fever, malaise, cellulitis and/or lymphadenopathies) following adequate endodontic disinfection and abscess drainage if swelling is present[8, 9]. In addition, patients who are immunocompromised or have predisposing conditions such as previous endocarditis should be medicated as a prophylactic measure. It is important to note that administration of antibiotics in the absence of the above-mentioned reasons has no evidence of therapeutic benefit [10, 11]. Lastly, in the cases of a therapeutic indication, the choice of the antibiotic agent, dosage and duration is typically made in an empirical fashion.

Penicillin VK and amoxicillin, both beta-lactam antibiotics, are the first line of antibiotics chosen as adjunct therapeutic agents in endodontics in the United States of America and Europe.[12, 13] These drugs act by binding and inhibiting the activity of several bacterial proteins called penicillin binding proteins (PBP) involved in the synthesis of the peptidoglycan cell wall in susceptible both gram-positive and gram-negative bacteria[14]. These drugs have been found to be highly effective against isolates from infected root canal systems that are composed primarily of facultative and obligate anaerobes.[15, 16, and 17.]

Amoxicillin demonstrates greater efficacy and therapeutic value because:

- It has broader spectrum and is more effective than penicillin VK against certain gram-negative anaerobes due to better microbial penetration;
- It is more readily absorbed from the gastrointestinal (GI) tract than penicillin VK, which is poorly absorbed and its accumulation in the GI tract is associated with depletion of commensal flora and digestive disturbances
- Its absorption is not impaired by food reaching peak plasma levels within 2 hours of ingestion;

- Only approximately 20% of absorbed amoxicillin is protein-bound in the plasma, being more readily available;
- It has significantly greater half-life than penicillin VK requiring doses to be taken 2-3 times a day as opposed to 4 times daily for penicillin VK [14].

The recommended dose regimen for amoxicillin is 500 mg three times a day (with or without a loading dose of 1,000 mg) for adults. Although these doses are well established based on pharmacokinetic studies and designed to establish maximum effective doses in the plasma, there is far less evidence to support the duration of treatment. Most practitioners usually prescribe antibiotics in courses of 3 to 7 days[18, 19]. Interestingly, some evidence suggests that perhaps shorter courses (2-3 days) may be successfully used as adjuvant therapies. The decision of using antibiotics for longer periods (7 to 10 days) is largely based on studies and clinical practice of treating infections whose etiology is not fully identified or the treatment of bloodstream infections in hospitalized patients. This clinical indication and use of antibiotics differ from the endodontic use as an adjunct therapy to limit the spread and the systemic manifestation of the infection following adequate surgical debridement and establishment of drainage. Moreover, therapies lasting 7 days with amoxicillin have been shown to increase the population of resistant strains (32). It is estimated that approximately 30% of severe dento-alveolar infections have strains resistant to penicillin-like drugs[20]. Increased presence of resistance strains has been associated with over prescription of this class of drugs.

This indiscriminate antibiotic use has selected strains that possess many resistance mechanisms against beta-lactam antibiotics. These include:

- Constitutive expression of high molecular weight penicillin-binding proteins (PBP) that have lower affinity to beta-lactam antibiotics;
- Expression of beta-lactamase (also known as penicillinase) enzymes and
- Drug efflux pumps, particularly in certain gram-positive strains

For this reason, if symptoms are not improved after endodontic debridement and/or drainage, amoxicillin may be combined with clavulanic acid (125 mg bid or tid), which is a beta-lactamase inhibitor and increases the susceptibility of penicillin resistant strains. This combination has been shown to be effective against 100% of cultivable endodontic bacteria, increasing the spectrum of amoxicillin in persistent infections. However, the use of amoxicillin/clavulanic acid combinations should not be done indiscriminately as there are potentially significant side effects that include gastrointestinal and hepatic disturbances[20].

In susceptible patients, immunoglobulin E (IgE) against breakdown products of penicillin is readily detected in patients with a history of penicillin allergic reactions (40). Anaphylactic types of reactions are the most severe manifestation of allergy to beta-lactam antibiotics but are the least prevalent. Thus, these drugs should be avoided in patients with a previous history of hypersensitivity, or discontinued in patients without a history but with presentation of hypersensitivity, to avoid life-threatening anaphylactic reactions.

Clindamycin is the first drug of choice for patients with a history of hypersensitivity to penicillin drugs. This drug is a lincosamide antibiotic that acts by binding to the 50S ribosomal subunit, suppressing protein synthesis. Therefore, its effects are mainly bacteriostatic, although bactericidal effects can be achieved with therapeutic doses. It has been shown to be effective against 75% of cultivable endodontic pathogens. It has very good spectrum, with coverage against both facultative and obligate anaerobic bacteria.

Clindamycin is readily absorbed after oral administration, which is not impaired by concomitant food consumption, reaching peak plasma levels in 1 hour (9 μg/ml after a loading dose of 600 mg in adults). The drug is widely distributed in the body, including bone (44). The recommended dosage for infections of endodontic origin is 600 mg as a loading dose followed by 300 mg every 6 hours, whereas in children, this dose must be adjusted to 10-30mg/Kg (dose/ body weight) divided into 4 equal doses.

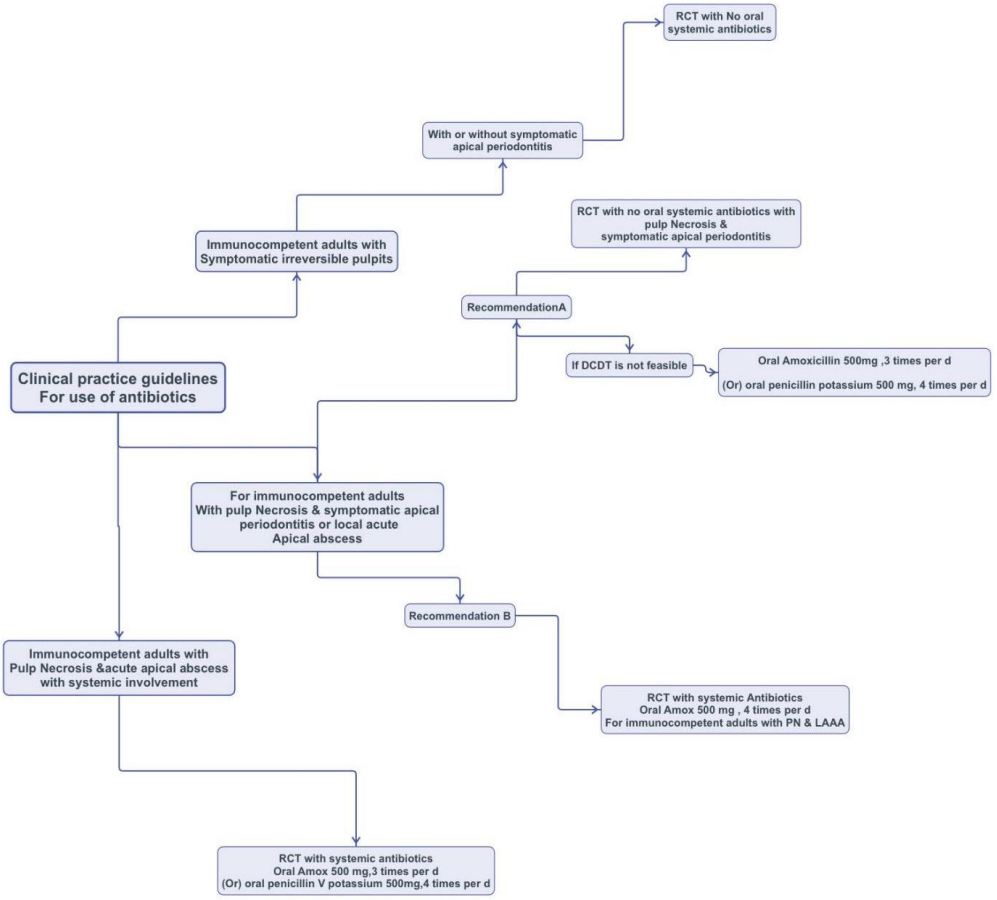
Despite its excellent pharmacokinetics and moderate effectiveness against endodontic pathogens, its use can be associated with significant side effects. Gastrointestinal disturbances are the most common side effect with an approximately eight-fold increased risk of developing C. difficile infection than the use of penicillin that can evolve into pseudomembranous colitis, a potentially fatal disease. Thus, administration of this drug must be discontinued upon the first signs of this disease (i.e. diarrhoea with fever, abdominal pain, mucus and blood in the stool) and the patient referred to a primary care physician for treatment that may involve prescription of metronidazole orally or intravenously.

Caution should be employed when prescribing this medication for patients with history of clindamycin-associated pseudomembranous colitis. Thus, patients with a history of penicillin allergy and severe gastrointestinal reactions to clindamycin require alternative antibiotics such as macrolides, quinolones or tetracycline. Unfortunately, endodontic pathogens have lesser susceptibility to these alternative antibiotics with increased prevalence of resistant strains. (Flow chart 1)

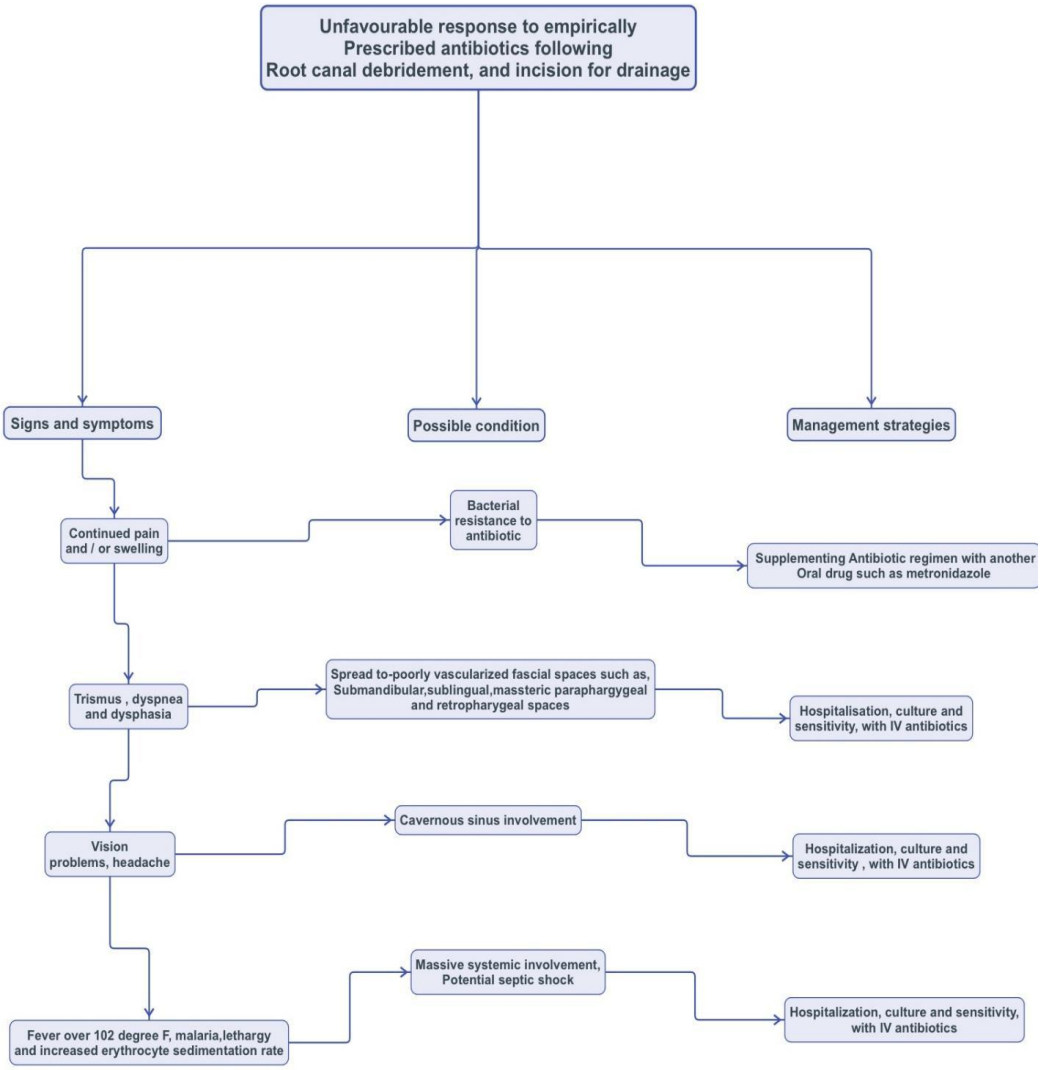
Use of Antibiotics in the absence of adequate debridement and surgical drainage

There is evidence from randomized clinical trials and systematic reviews to indicate that supplemental antibiotics following adequate debridement and drainage in cases of localized endodontic infections is ineffective. It is also the standard of care to prescribe primary or adjunctive antibiotics in conjunction with local debridement and surgical drainage for patients who have spreading infections, and to monitor their progress closely as these prescriptions are made empirically and may be ineffective or insufficient for adequate treatment. Efficacy or duration of antibiotics for cases in which the practitioner is not able to render local debridement and drainage at the time of patient presentation, or in cases that are complex and the efficacy of local treatment may not be completed. In these cases, it is not known whether systemic antibiotic therapy would provide sufficient relief of symptoms and prevention of spread of infection to warrant a prescription, since etiology of the infection may not have been fully addressed.

Dentists and endodontists must weigh the benefits and risks of antibiotics, and make an informed decision with their patients on the appropriateness of using antibiotics in such cases. One strategy that may be useful is to educate the patient about the signs and symptoms of a spreading infection and give the patient a “stand-by” antibiotics prescription (Flow chart 2)



Flow chart 1: clinical practice Guidelines for use of Antibiotics in Endodontics



Flow chart 2: Antibiotics prescribed following Root canal debridement, and incision for drainage

Prophylactic use of antibiotics for endodontic surgery

Prophylactic use of antibiotics to prevent postoperative infections is common in general and oral surgery. Factors involved in the decision of whether to prescribe prophylactic antibiotics, and whether to provide one preoperative dose or a prolonged course, include the type and site of surgery, the morbidity associated with potential infection, and the systemic health of the patient. One randomized clinical trial compared giving 256 patients undergoing endodontic surgery either preoperative 600 mg tablet of clindamycin or placebo (51). The results were that four patients in the placebo group and two in the clindamycin group developed postoperative infection, and this difference was not statistically significant.

However, the average surgical time in this study was only about 30 minutes in both groups, and the overall number of infections was low. There are no data available for endodontic surgery that may take a longer period or are performed in practices that have higher rates of postoperative infections. Nevertheless, there is evidence that antibiotic prophylaxis may reduce postoperative infection following exodontia and surgical osteotomy extraction (52, 53). In addition, there is one study that showed that peri-operative antibiotic prophylaxis significantly reduced the incidence of bisphosphonate-related osteonecrosis of the jaw, in multiple myeloma patients on IV bisphosphonates undergoing dental surgery (54). In cases where the biopsy result indicates periapical actinomycosis infection, it does not appear that antibiotic treatment is indicated, as the surgical procedure is associated with curettage of the infected tissues in these cases (55).

Association between adjunctive antibiotics and periapical Healing

The effect of perioperative antibiotics on long term healing of nonsurgical and surgical endodontics has not been sufficiently studied. One study compared the healing of apical periodontitis in 62 patients who underwent nonsurgical root canal treatment (56). There was no difference between the penicillin and the control groups in healing. A more recent endodontic prospective cohort study showed no association between the use of long term antibiotics and nonsurgical treatment or retreatment outcome.

Systemic Use of Antibiotics

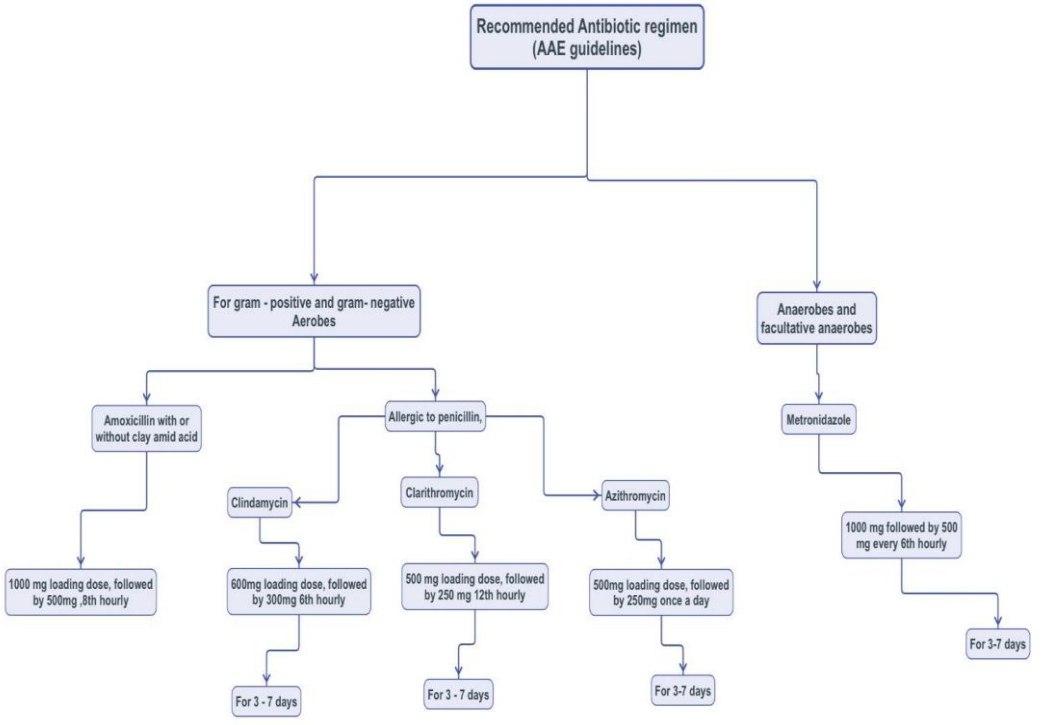
Antibiotics are proven to be ineffective in necrotic pulp, irreversible pulpitis and localized acute apical abscess as these conditions present with either restricted or total loss of vascularity, intercepting the delivery of these antibiotics to the site of concern. Cope et al, 2014 in his systemic review has concluded that the use of antibiotics in symptomatic apical periodontitis and acute apical abscess was of no value [9]. A thorough debridement of the canal to eliminate the microorganism and incision and drainage in case of discrete and localized swelling itself would be sufficient. On the other hand, adjunctive uses of antibiotics in certain conditions are useful as they help to contain the infection from spreading, thereby promoting healing. Acute apical abscess with systemic involvement or showing signs of spreading into interstitial spaces causing cellulitis are a clear indication for prescribing antibiotics. [10] In case of traumatic avulsion of tooth, current guidelines suggest the use of systemic antibiotics; however their efficacy has not yet been demonstrated by clinical studies. Local application has a positive effect, shown to improve healing of pulpal and periodontal tissues and prevents inflammatory root resorption. [11]

Commonly used Antibiotics and their recommended dosage and duration

Proper selection of antibiotics with correct dose, duration and frequency is important to avoid the development of resistant strains of bacteria. Amoxicillin is the most commonly used antibiotic for odontogenic infections.[12] It is a moderate spectrum, β lactam antibiotic effective against most of the aerobic gram positive and gram negative organisms. It has a longer half-life, better absorption rate than Penicillin [13].However, it is readily degraded by β lactamase producing organism

present in the gut, therefore is administered along with clavulanic acid to enhance its bioavailability. Its recommended loading dose is 1000mg, followed by 500mg every eight hours to obtain a steady serum level. (AAE 1999) (Flow chart 3)

In patients with penicillin allergy, alternative antibiotics like clindamycin, azithromycin or erythromycin can be prescribed.[14] Clindamycin is effective against most gram positive aerobes and both gram positive and gram negative facultative anaerobes. Recommended dosage is 600mg of loading dose followed by 300 mg every sixth hourly (AAE 1999). Metronidazole is given along with amoxicillin due to its excellent activity against anaerobes. Metronidazole in combination with amoxicillin has increased the susceptibility to 99% of bacteria.[15] The adult oral dose is 1000mg loading dose followed by 500mg every sixth hourly. (AAE 1999).Duration of an antibiotic course varies from 3 to 7 days. Ideally after 2 or 3 days of commencement of antibiotic course, the patient should be reviewed clinically, if there is clinical evidence of healing or betterment of patient's symptoms, the antibiotics can be discontinued. (AAE 1999)

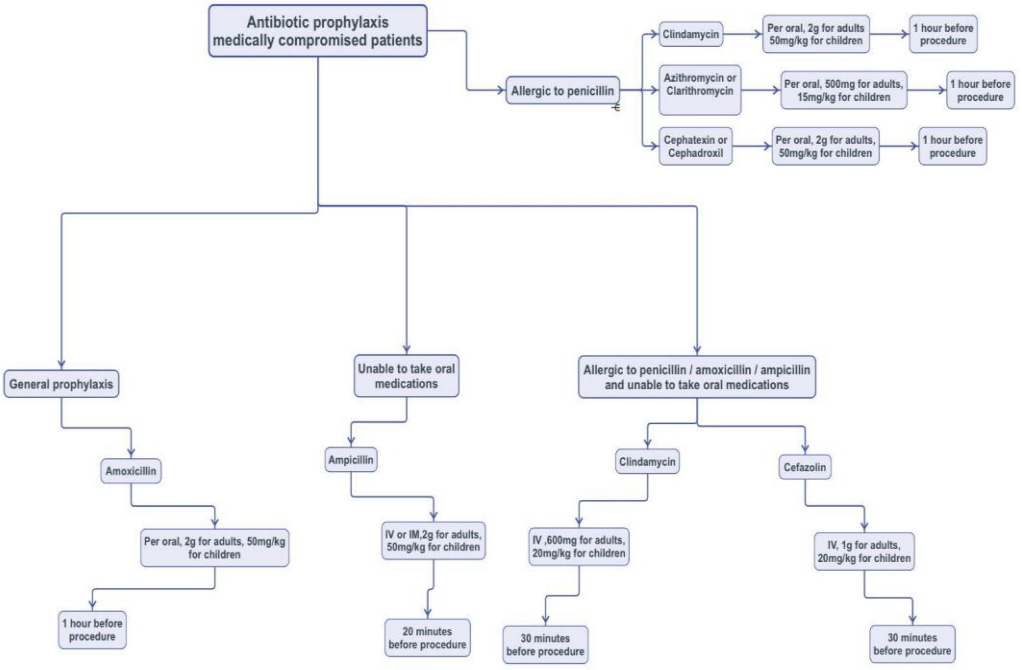


Flow chart 3: Recommended Anibiotics, their dose, Frequency and Duration

Antibiotic Prophylaxis

In healthy individuals, the risk of dissemination of infection through bloodstream is prevented by scavenging of microorganism by immune cells. But patients with immunocompromised conditions, like leukemia, HIV/AIDS, chronic disease. etc.

and those with infective endocarditis, prosthetic heart valves and congenital heart diseases and patient undergoing chemotherapy or radiotherapy may require antibiotic prophylaxis before dental procedure. [16] Antibiotics should be given prophylactically only when their benefits overweighs their risks. Antibiotic prophylaxis should be given for infective endocarditis patients following an invasive dental procedure involving manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa and root canal procedures (European Society of Cardiology 2015).[17,18,19]. For patients requiring endodontic therapy within the first 3 months of prosthetic joint replacement surgery, antibiotic prophylaxis should be considered.[20] Endodontic treatment of cancer patients exposed to high dose irradiation of head and neck should be precede by antibiotic prophylaxis.[21]



Flow chart 4: Antibiotics prophylaxis for medically compromised patients

Topical Use of Antibiotics

Several antimicrobial formulations have been used during endodontic treatment, either in the form of liquids (irrigating solutions), pastes (intracanal medicaments) or solids (obturating materials). The rationale for the local application of antibiotics is that there is no definitive evidence that mechanical instrumentation alone results in bacteria free root canal system. Therefore the use of antimicrobial agents aims to eliminate the microorganisms present in the complexities of root canal systems, like isthmus, accessory canals, lateral canals, fins, deltas which are inaccessible to mechanical instrumentation.[22] Antimicrobial agents are used

either in the form of chemical antiseptics or antibiotics. Chemical antiseptics are very effective in killing microorganisms but at the same concentration can cause toxicity to host cells itself, therefore its use should be limited to short term contact, e.g., irrigating solutions (EDTA, sodium hypochlorite, chlorhexidine). Antibiotics kill microorganism by acting during the cell reproductive cycle, they are less toxic and tolerable by host cells, therefore indicated for prolonged contact time, therefore suitable as intracanal medicaments.[23] The first reported use of antibiotics in endodontics was by Grossman in 1951, PBSC polyantibiotic paste contacting Penicillin, Bacitracin, Streptomycin and Caprylate sodium. Later Nystatin replaced caprylate which was then known as PBSN. [24]

Tetracyclines

Tetracycline including tetracycline HCl, doxycycline, demeclocycline, and minocycline are broad spectrum antibiotics that are bacteriostatic in nature. Other than antimicrobial property, they have unique properties of inhibiting the collagenase enzyme, which is responsible for tissue destruction and also it is said to inhibit the clastic cell activity, thereby preventing resorption. [25] Tetracycline irrigant has shown to have excellent smear layer removing property. A SEM study assessing the smear layer removing ability reported that tetracycline was as effective as citric acid.[26] Carson et al, compared the antimicrobial effectiveness of 3% and 6% NaOCl, 2% and 0.12% CHX and 0.01% and 0.005% doxycycline against four endodontic pathogens concluded that 0.01% doxycycline had superior antimicrobial efficacy followed by 0.005% doxycycline. [27] In case of traumatic avulsion of tooth, placing the tooth in doxycycline solution (1mg in 20ml of saline for 5 minutes) reduces the frequency and severity of inflammatory root resorption and increases the success of pulp revascularization [28,29] Substantivity of tetracycline has shown to last upto 12 weeks.[30]

Triple Antibiotic paste

Due to the diversity of endodontic microbiology, combination of antibiotics is suggested to be more effective. Sato et al, first used triple antibiotic paste in a combination of metronidazole, ciprofloxacin and minocycline in propylene glycol base which had excellent antimicrobial efficacy against root canal flora. [38] The recommended ratio is 1:1:1of metronidazole (500 mg), minocycline (100 mg) and ciprofloxacin (200 mg).[39] The formulation was modified by Takushige *et al.*, to a ratio at 3:3:1.[40] Cefaclor can be used to prevent the discolouration caused by minocycline[41

MTAD

MTAD is a mixture of tetracycline, an acid and a detergent introduced by Torabinejad and Johnson in 2003. It consists of 3% doxycycline, 4.25% citric acid and 0.5% polysorbate 80 (detergent). MTAD when used as irrigant is able to remove smear layer and is shown to be effective against *E.faecalis*.[31] MTAD as a final irrigant was preferred due to its property of substantivity that lasted upto 4 weeks.

However, Tay et al reported that antimicrobial efficacy and substantivity of MTAD reduced when used on NaOCl irrigated dentin, due to oxidation of MTAD by tetracycline.[32] The use of MTAD as final irrigant is still controversial.

Ledermix paste

As developed by Schroeder and Triadan in 1960, it is a combination of 3.2% demeclocycline HCl and 1% triamcinolone acetonide in polyethylene glycol base. It is capable of diffusing through the dentinal tubules to reach the periapical and periradicular tissues. Abbott et al, has reported that the concentration of demeclocycline in high enough within the root canals to kill susceptible species of bacteria, but the concentration of the drug that is achieved through diffusion in cementum and periradicular tissues is insufficient to inactivate bacteria, especially over time.[33] In an animal study by Bryson et al, he compared the effect of placing ledermix paste and CaOH in root canals of dog teeth that was replanted after 60 minutes of extra oral dry time, it was seen that Ledermix group had better healing and less resorption. Clinical trial by Ehrmann et al, reported that the postoperative pain followed by placement of ledermix paste was significantly lesser than CaOH. Ledermix paste is restricted below gingival margin within the root canals because of its ability to cause discolouration when exposed to sunlight.A 50:50 mixture of ledermix paste and CaOH is advocated as it results in slower diffusion and prolonged antibacterial efficacy and is indicated in case of perforations inflammatory root resorption, periapical bone resorption, and large periapical radiolucency.

Conclusion

Use of antibiotics is not a necessity for all endodontic cases, therefore judicious and appropriate usage of antibiotics will help contain infection and prevent the development of antibiotic resistance and the adverse effects cause by antibiotic overdose.

References

1. Enriquez FJJ, Vieyra JP and Ocamp FP. Relationship between clinical & histopathological findings of 40 periapical lesions. Dentistry .2015:5(2);1-7
2. Levin LG, Law AS, Holland GR, Abbott PV and Rodo RS. Identify and define all diagnostic terms for pulpal health and disease states. J Endod 2009; 35:1645-57.
3. SBen P, Cotti, Mazzari A, Sumay H, Tjadhane L, Dummer PM,, European society of Endodontology position statement : the use of antibiotics is endodontics.
4. Cohen, S &Burns , R.C. Pathway of the pulp (Mostly St Louis2002)
5. DaileyY.M &Martin m,v. Are antibiotics being used appropriately for emergency dental treatment? British dental journal 191,391-393(2001)
6. Harison, J.W&Svec. T.A. The beginning of the end of the antibiotic era. The problem abuse of the 'Miracle drugs"
7. Konig C, Simmen HP, Blaser J. Bacterial concentrations in pus and infected peritoneal fluid--implications for bactericidal activity of antibiotics. J Antimicrob Chemother 1998; 42:227-32.

8. Matthews DC, Sutherland S, Basrani B. Emergency management of acute apical abscesses in the permanent dentition: a systematic review of the literature. J Can Dent Assoc 2003;69:660.
9. Aminoshariae A, Kulild JC. Evidence-based recommendations for antibiotic usage to treat endodontic infections and pain: A systematic review of randomized controlled trials. J Am Dent Assoc 2016;147:186-91
10. Fouad AF, Rivera EM, Walton RE. Penicillin as a supplement in resolving the localized acute apical abscess. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 81:590-5.
11. 11.Walton RE, Chiappinelli J. Prophylactic penicillin: effect on post treatment symptoms following root canal treatment of asymptomatic periapical pathosis. J Endod 1993; 19:466-70.
12. Segura-Egea JJ, Gould K, Sen BH, Jonasson P, Cotti E, Mazzoni A, et al. Antibiotics in Endodontics: a review. Int Endod J 2016
13. Rodriguez-Nunez A, Cisneros-Cabello R, Velasco-Ortega E, Llamas-Carreras JM, Torres-Lagares D, Segura-Egea JJ. Antibiotic use by members of the Spanish Endodontic Society. J Endod 2009;35:1198-203.
14. Wright AJ. The penicillins. Mayo Clin Proc 1999;74:290- 307.
15. Pinheiro ET, Gomes BP, Ferraz CC, Teixeira FB, Zaia AA, Souza Filho FJ. Evaluation of root canal microorganisms isolated from teeth with endodontic failure and their antimicrobial susceptibility. Oral Microbiol Immunol 2003;18:100-3
16. Khemaleelakul S, Baumgartner JC, Pruksakorn S. Identification of bacteria in acute endodontic infections and their antimicrobial susceptibility. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94:746-55.
17. Jungermann GB, Burns K, Nandakumar R, Tolba M, Venezia RA, Fouad AF. Antibiotic resistance in primary and persistent endodontic infections. J Endod 2011;37:1337-44
18. Segura-Egea JJ, Velasco-Ortega E, Torres-Lagares D, Velasco-Ponferrada MC, Monsalve-Guil L, LlamasCarreras JM. Pattern of antibiotic prescription in the management of endodontic infections amongst Spanish oral surgeons. Int Endod J 2010;43:342-50.
19. Palmer N, Martin M. An investigation of antibiotic prescribing by general dental practitioners: a pilot study. Prim Dent Care 1998;5:11-4
20. Nikaido H. Antibiotic resistance caused by gram-negative multidrug efflux pumps. Clin Infect Dis 1998;27 Suppl 1:S32-41.
21. Mahalakshmi Nandakumar. Use of Antibiotics in Endodontics.Research.pharm and Tech. 12.jan 2019