

Updated Guidelines Regarding Antimicrobial Resistance in Dentistry: A Concise Review

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Abstract

Dental caries, periodontal diseases, trauma, pulp necrosis can lead to odontogenic infections with symptoms like pain, inflammation, fever, abscess, pus discharge. These odontogenic infections need surgical or non-surgical treatment approaches with antibiotics. Antibiotics were popularized as “wonder drug” and a boon to society initially. Newer antibiotics are introducing in market very rapidly which leads to advent of resistant bacteria. Bacterial resistance develops very fast and that is the biggest concern. There is no control on use of antibiotics and its worldwide major problem. In this paper we will do a comparison among the guidelines for antibiotics use of various countries as well as review of literature. Data for the research will be collected from the indexed articles and documents by

officials for the antimicrobial prescription in dentistry by using word ‘antibiotics’, ‘antibiotic resistance’, ‘antimicrobial in dentistry’ on internet. This paper will provide a guide to dentists before prescribing antimicrobials. All guidelines convey a single message that antimicrobials should be measured and administered properly. Use of antimicrobials should be restricted only to critical conditions for compromised patients. Antimicrobial administration should be examined by officials as it seems vague and its application is also wide spread, according to some research studies use of antimicrobials is not just restricted to critical conditions as given by the guidelines. The pediatricians, the general practitioners and the dentists should take accurate precaution and be aware while administering

antimicrobials, in cases which are recommended by the guidelines as safe and beneficial.

Keywords: Antimicrobials, Antibiotics, Antibiotic Resistance, Guidelines

Introduction

In the mid - 20th century antimicrobials were popularized as the 'wonder drug'. Antibiotics are a boon for a human civilization to fight against infections and microorganisms which saved many people lives. Antibiotics with various type of actions against different microorganisms are available in market. At the time, there was an optimistic belief that disease was nearly coming to an entire halt. The 'era of antibiotic' is mainly recalled by two scientists' names Alexander Fleming and Paul Ehrlich.¹ A word 'magic bullet' was contemplated for antibiotics as it acts against specific microorganisms which cause disease and would not exert any effect on host. Potential resistance to penicillin was first observed by Fleming if used too little or for a too short period of treatment.¹ Antibiotics either are cytotoxic or cytostatic to the micro-organisms, allowing the body's natural defenses, like the system, to eliminate them. Antibiotics act by inhibiting the synthesis of a bacterial cell, proteins (deoxyribonucleic acid (DNA), ribonucleic acid (RNA)) synthesis, by a membrane disorganizing agent, or other specific actions.² Antibiotics may also enter the cell wall of the bacteria by binding to them, using the energy-dependent transport mechanisms in ribosomal sites, which subsequently leads to the inhibition of the protein synthesis.³ The period from the 1950s to 1970s was thus considered as the golden era for the discovery of novel antibiotics classes.⁴

Global antibiotic consumption rose by 46% between 2000 and 2018, and the BRICS countries (Brazil, Russia, India, China, South Africa) accounted for about three-

quarters of this consumption.⁵ Bacterial resistance is the capacity of bacteria to withstand the effects of antibiotics that are intended to kill or control them.⁶ antimicrobial resistance is a normal evolutionary process for microorganisms, it is accelerated by the widespread use of antimicrobials. Evidence suggests a clear link between the levels of antimicrobial use and the development of antimicrobial resistance.⁷

With an abundance of evidence, there's no scope to ignore global antibiotic resistance. Antibiotic resistance is often more prevalent where antibiotic consumption is found to be higher. Lack of regulation and control in using antibiotics is prominent and wishes to be targeted at a worldwide capacity. Developing nations are at the greatest risk. Low prices of antibiotics, ease of availability and unnecessary use of antibiotics are causing more burden in developing countries.² Antibiotic use is relatively uncontrolled among the countries where there is no universal health coverage for its citizens.⁸ Hence, irrational use of drugs has become a major concern. According to a study wiped out the uk, among the participants, 11.3% reported that they didn't finish their last antibiotic course as prescribed. When asked about the reason why not comply with the course, 65% of the respondents stated that they felt better or forgot to take an antibiotic in time.⁹ Antimicrobial resistance is spreading to such an extent that it should be addressed urgently and globally, WHO and various other studies also complies to same and onset of antibiotic resistance is also shown in figure 1.¹⁰

In the developing world, most the antibiotics are available over the counter and may be bought with none medical prescription which is one among the foremost important factors in causing the resistance. Therefore, if the resistance to the antibiotics must be curbed, the sole way shall be to teach the patients and therefore the

general public and form guidelines for antibiotics prescription for dentists.¹⁰

In this review, we aim to provide some applicable data for dentists to prescribe appropriate types of antibiotics and various countries guidelines for it.

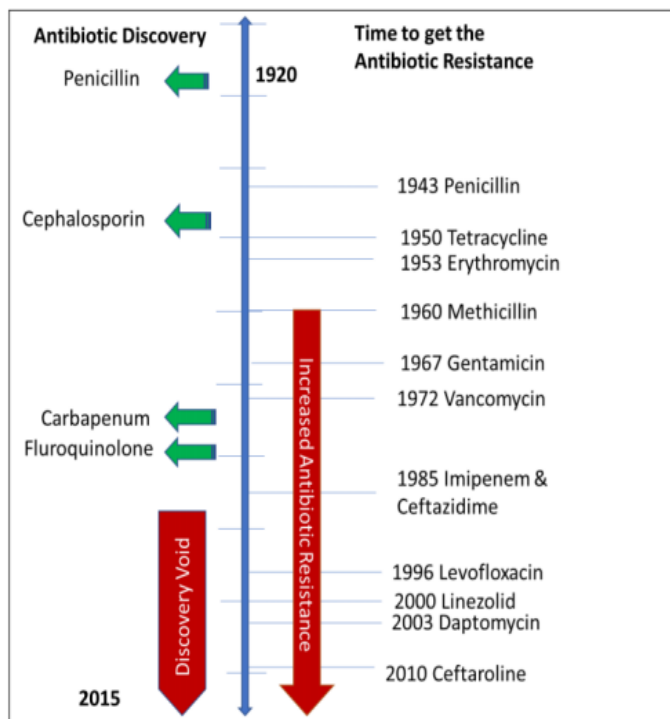


Figure 1³⁰: Graphical representation of onset of antibiotic resistance versus time to get antibiotic resistance

History of antibiotic discovery (green arrow) and time of first reported year of antibiotic resistance (right side). The red arrow (lower direction) indicates the discovery void and increased antibiotic resistance. The blue line indicates the time flow.

Source: Zaman S, Hussain M, Nye R, et al. (June 28, 2017) A Review on Antibiotic Resistance: Alarm Bells are Ringing. *Cureus* 9(6): e1403.

Antibiotics frequently prescribed by dentists

One of the kinds of antibiotics most utilized in dentistry is represented by penicillin. This antibiotic is employed within the sort of amoxicillin and clavulanate in most cases of prescription. Other antibiotics mostly

used, according to current guidelines, are metronidazole (in periodontology only), azithromycin, clindamycin, clarithromycin, doxycycline, and erythromycin and are also enlisted in table 1.

Penicillin

Penicillin was discovered from *Penicillium notatum* which is a narrow spectrum antibiotic. The most common sorts of penicillin that are being administered for treatment of odontogenic infections are penicillin V, amoxicillin, and amoxicillin/clavulanic acid, and studies show that they require almost the same efficacy for the treatment of dental infections. Aminopenicillins are one of the three antibiotic types most commonly prescribed in dentistry.¹¹ Amoxicillin resistance has been described in *Veillonella* spp. and *Prevotella denticola* isolated from root canals. According to previous investigations, nearly 70% of bacteria isolated from odontogenic infections were susceptible to penicillin.¹² Commonly, penicillin is considered to be the first-line drug and the gold standard for the treatment of odontogenic infections due to its cost-effectiveness, low incidence of side effects, and appropriate antimicrobial activity.

Amoxicillin

Amoxicillin may be a penicillin antibiotic that acts against Gram-negative bacilli. Amoxicillin is usually considered to be the primary line of treatment in nonallergic patients. It is prescribed more frequently than other antibiotics. Some practitioners also prescribe the combination of metronidazole and amoxicillin or amoxicillin/clavulanate to treat odontogenic infection. The therapeutic dosage for amoxicillin is 500 mg every 8 hours or 1000 mg every 12 hours.¹³

Amoxicillin with Clavulanic Acid (Co-Amoxiclav)

Amoxicillin with clavulanic acid (co-amoxiclav) is a broad-spectrum antibiotic that's believed to be the second most prescribed antibiotic by dentists. All the

bacteria which exist in odontogenic infections are susceptible to this combination.¹⁴

Cephalosporin

Cephalosporins are classified in beta lactam antibiotics and may inhibit the biosynthesis of bacterial cell walls. Cephalosporins target against aerobic bacteria, and their combination with metronidazole could act against both aerobic and anaerobic bacteria. Cephalexin and Cefazolin are among the foremost commonly prescribed first-generation Cephalosporins in practice.¹⁵

Metronidazole

Metronidazole has bactericidal activity and acts against anaerobic microorganisms by inhibiting the macromolecule synthesis; the agent also showed antiprotozoal activity and doesn't disrupt the protective aerobic microbiota. Combined administration of amoxicillin and metronidazole could act against almost all the oral bacteria. Prescribing this combination or metronidazole is also advised for the treatment of periodontal diseases.¹⁶

Erythromycin

Erythromycin has bacteriostatic activities and is usually prescribed for cavity and bacterial plaque. The most common microorganism that causes cavity is *Streptococcus mutans*, which is very sensitive to erythromycin. Erythromycin may inactivate the caries, and can decrease the growth and dental plaque formation.¹⁷

Azithromycin

Azithromycin may be a bacteriostatic antibiotic that features a great potency against Gram-negative pathogens and is taken into account to be the safest among the macrolides. It is not advised as the first-line of treatment for odontogenic infections and is commonly prescribed as a substitute in penicillin-allergic patients.¹⁸

Clarithromycin

Clarithromycin may be a broad-spectrum antibiotic that's considered to be the new generation of erythromycin. Clarithromycin may be a bacterial protein synthesis inhibitory and matrix metalloproteinase (MMP) regulating activities that would fight against intracellular pathogens by penetrating the cells. Among the macrolides, the agent is believed to possess the best effect against anaerobic Gram-positive bacilli. Hence over, the prescription of clarithromycin is often a logical approach for suppressing the pulp and periodontal infections. However, clarithromycin is not usually recommended as the first-line treatment and is used instead of penicillin in patients who cannot tolerate the gold standard treatment of penicillin.¹⁹

Tetracyclines

Tetracycline may be a bacteriostatic antibiotic that's active against Gram-positive and Gram-negative bacteria, acting by blocking the synthesis of protein through binding to the ribosomal subunit. The drug might be an inexpensive prescription for the treatment of periodontal diseases, because it has anti-inflammatory activity, Collagenase inhibition potential, and bone resorption inhibitory capacity; besides, it could help the fibroblasts to connect to the basis surface. Tetracycline is prescribed in periodontal diseases which improves marginal attachment. It has a long half-life, maintains its antimicrobial activity for a long period, and is released from the tooth surface slowly.²⁰

Table 1: Most frequently prescribed antibiotics in dental practices.

Antibiotic	Recommended Dose	Route Of Administration
Penicillin	1.2-2.4 Million IU/24 H (IV)Up To 24 million IU/24 Hours (IM)	IM Or IV
Amoxicillin	500 Mg/8 Hours 1000 Mg/12 Hours	Oral
Amoxicillin + Clavulanic Acid	500-875 Mg/8 Hours (Oral) 2000 Mg/12 Hours (Oral) 1000-2000 Mg/8 Hours (IM)	Oral/IV
Cephalosporin	25–100 Mg/Kg/Day	Oral
Metronidazole	500-750 Mg/8 Hours	Oral
Azithromycin	500mg/24hours 3 Consecutive Days	Oral

Guidelines for prescribing antibiotics

1. American dental association guidelines²¹

➤ Clinical pathway for treatment of immunocompetent adult patients seeking treatment during a dental setting with a pulpal or periapical condition, during which definitive, conservative dental treatment (DCDT) isn't immediately available. Treatments mentioned under DCDT are pulpotomy, pulpectomy, nonsurgical root canal treatment, or incision for drainage abscess. Only clinicians who are authorized or trained to perform the required treatment should do so. Clinical pathway for treatment of immunocompetent

adult patients seeking treatment in a dental setting are shown in fig 2&3

- Adult patients with pulp necrosis and symptomatic apical periodontitis should be informed to call if their condition deteriorates (progression of disease to a more severe state) or if the referral to receive DCDT within 1-2 days is not possible.
- For adult patients with pulp necrosis and symptomatic apical periodontitis, a delayed prescription should be provided if DCDT isn't immediately available.
- Dentists must communicate to their patients that if their symptoms worsen and they experience swelling, the delayed prescription should be immediately filled.
- A delayed prescription is defined by the Centres for Disease Control and Prevention as a prescription that's used for patients with conditions that sometimes resolve without treatment but who can get results from antibiotics if the conditions do not improve.
- Clinicians should re-evaluate within 3days (for example, in-person visit or phone call). Dentists should instruct patients to discontinue antibiotics 24h after their symptoms resolve, regardless of re-evaluation after 3days.
- Although the expert panel recommends both amoxicillin and penicillin as first-line of drugs, amoxicillin is recommended over penicillin because it is more effective against various gram-negative anaerobes and is associated with lower incidence of gastrointestinal adverse effects.
- Bacterial resistance rates for azithromycin are more than for other antibiotics, and clindamycin substantially increases the danger of developing Clostridioides difficile infection even after a single dose.
- Owing to concerns about antibiotic resistance, patients who receive azithromycin should be instructed to closely monitor their symptoms and call a dentist or

medical care provider if their infection worsens while receiving therapy.

- Similarly, clindamycin features a US Food and Drug Administration black box warning for Clostridioides difficile infection, which may be fatal.
- Patients should be instructed to call their medical care provider if they develop fever, abdominal cramping, or ≥ 3 loose bowel movements.
- If the patient is apparently taking an antibiotic within the equivalent spectrum as per indication, additional antibiotics need not be prescribed.
- If the patient currently is taking an antibiotic outside of the spectrum as the one indicated, the intended antibiotic still can be prescribed, considering potential contraindications. An antibiotic with an identical spectrum of activity to those recommended can be continued if the antibiotic was initiated before the patient sought treatment. As with any antibiotic use, the patients should be told about symptoms which will indicate lack of antibiotic efficacy and adverse drug events.

Figure 2²¹: Clinical pathway for treatment of immunocompetent adult patients seeking treatment in a dental setting with a pulpal or periapical condition, in which definitive, conservative dental treatment (DCDT) is not immediately available.

Source - Peter B. Lockhart, Malavika P. Tampi, Elliot Abt, Anita Aminoshariae, Michael J. Durkin, Ashraf F. Fouad, Prerna Gopal et al. the urgent management of pulpal- and periapical-related dental pain and intraoral swelling A report from the American Dental Association, Volume 150, Issue 11, P906-921.E12, November 01, 2019

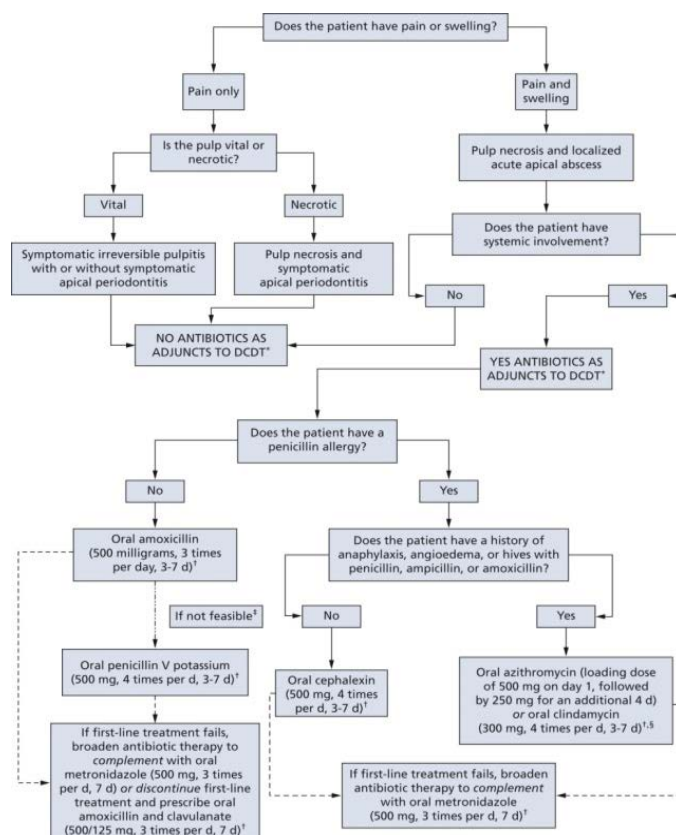


Figure 3²¹: Clinical pathway for treatment of immunocompetent adult patients seeking treatment in a dental setting with a pulpal or periapical condition, in which definitive, conservative dental treatment (DCDT) is immediately available.

Source - Peter B. Lockhart, Malavika P. Tampi, Elliot Abt, Anita Aminoshariae, Michael J. Durkin, Ashraf F. Fouad, Prerna Gopal et al. the urgent management of

pulpal- and periapical-related dental pain and intraoral swelling. A report from the American Dental Association, Volume 150, Issue 11, P906-921.E12, November 01, 2019.

2. Canadian dental association guidelines²²

In Canada, approximately 92% of antibiotics are used outside of the acute care hospital setting; 89% are prescribed by physicians, 8% by dentists and 3% by nurses, pharmacists and optometrists. In dentistry, antibiotics are prescribed as prophylactic dose and therapeutic dose preferably. Prophylactic antibiotics are used to prevent infection and these sorts of prescriptions are more prevalent than those for therapeutic antibiotics, which are used to treat an existing infection. The Canadian Dental Association supports the American Heart Association's guidelines for antibiotic prophylaxis before certain oral health procedures to stop infective endocarditis on high-risk patients only.

3. California dental association guidelines²³

These guidelines developed as a framework for the judicious and appropriate use of antibiotics in the various outpatient settings in which antibiotics are prescribed for patient use.

Guidelines described as

- Correctly diagnose an oral bacterial infection.
- Consider therapeutic management interventions, which may be sufficient to fight against localized oral bacterial infection.
- Weigh potential benefits and risks (i.e., toxicity, allergy, adverse effects, Clostridium difficile infection) of antibiotics before prescribing.
- Never prescribe antibiotics for ulcerations related to aphthae or trauma, oral viral infections and fungal infections.

➤ Implement national antibiotic prophylaxis recommendations for the medical concerns for which guidelines exist (e.g., cardiac defects).

➤ Assess the patient's medical history and conditions, pregnancy status, drug allergies and potential for drug-drug interactions and adverse events, any of which may impact antibiotic selection.

➤ Make and document the diagnosis, treatment steps and rationale for antibiotic use (if prescribed) in the patient chart.

➤ Use the most targeted (narrow spectrum) antibiotic for the shortest duration possible (two to three days after the clinical signs and symptoms subside) for otherwise healthy patients.

4. National Institute for Health and Care Excellence (NICE) by UK²⁴

The indications for prescribing antibiotics in dental practice according to NICE are listed below:

➤ As an adjunct to surgical treatment of any acute or chronic infection.

➤ To treat active infective disease e.g., necrotizing ulcerative gingivitis.

➤ Where definitive treatment may be delayed due to referral to specialist services, e.g., inability to establish drainage in an uncooperative patient requiring sedation or general anesthetic.

➤ Rarely for prophylaxis.

5. Indian national guidelines²⁵

➤ The antibiotic therapy selected must be based on presumptive diagnosis made on some assumption regarding the nature of disease.

➤ Necessity for antibiotic treatment should be reviewed on a daily basis. For most infections 5 – 7 days of antimicrobial therapy is sufficient.

➤ When combinations are used, the choice of the drug should be that they act synergistically.eg 1.

Aminoglycoside and beta-lactam antibiotic. 2. Beta-lactam antibiotic and beta-lactamase inhibitor.

3. Beta-lactam antibiotic and Glycopeptide (vancomycin/teicoplanin)

4. Sulphamethoxazole and Trimethoprim.

6. Australian Guidelines²⁶

Key principles for dental antibiotic prescribing include the utilization of more narrow-spectrum agents with high oral bioavailability (clindamycin, doxycycline and metronidazole), using the shortest possible duration of therapy, based on the nature of the infection and the response of the patient to the treatment at 48–72 h postoperatively.

7. European Guidelines²⁷

According to the European Society of Endodontology, antibiotics can be prescribed in the following situations:

- Acute apical abscess in medically compromised patients.
- Acute periapical abscess with systemic involvement.
- Progressive infections.
- Replantation of avulsed permanent teeth.
- Soft tissue trauma requiring treatment.

On other way, consistent with the equivalent guidelines, administration of antibiotics should be avoided in the following situation:

- Symptomatic irreversible pulpitis.
- Pulp necrosis.
- Symptomatic apical periodontitis.
- Chronic apical abscess.
- Acute apical abscess without systemic involvement.

8. World Health Organization guidelines²⁸

The World Health Organization elaborated an integrated strategy so as to regulate and rationalize the utilization of antibiotics and prescriptions of physicians and dentists.

The resistance has got to be considered an intrinsic characteristic of bacteria, due to their long evolutive

history. A comparable characteristic has been described in anti-cancer fields, albeit it's a special phenomenon. The resistance is a proper evolution of bacteria, subsequently to the “nonnatural” selection induced by the antibiotics. A strategy to prevent and control antimicrobial resistance, including antibiotic resistance, was approved during the World Health Assembly in May 2015. This plan has the aim to make sure the prevention and treatment of infectious diseases with safe and effective medicines. The plan 5 objective strategies are:

- To improve awareness of antimicrobial resistance
- To strengthen surveillance
- To reduce the incidence of infections
- To optimize the use of antibiotics
- To guarantee investment in countering antimicrobial resistance.

So, considering the routine practice of dentists, the prescription of antibiotics must be safe and clinically advised by contemporary guidelines, as described in the previous paragraph. The dental surgery prophylaxis is based on the use of amoxicillin and clavulanate, to prevent endocarditis and problems for prosthetic joints patients. The most common procedures and pathologies of dental practice need not require antibiotics as elective or a treatment option. In fact, the American Dental Association guidelines are very cautious about antimicrobial prophylaxis in dentistry, same as the European and Italian ones.

9. Italian guidelines²⁹

In Italy, according to the last version of Clinical Guidelines in Dentistry, published by the Ministry of Health in September 2017, the use of antibiotics is suggested for the following situations:

- Systemic side effects after pediatric oral surgery
- Orthograde endodontic therapy, to reduce pain

- Tooth replantation
- Side effects of acute apical abscess
- Antimicrobial therapy for severe periodontitis.

Conclusion

Judicial and conscious prescription of antibiotics is necessary for the safe treatment. This will help in reduction of antibiotic resistance also. Dentists should have accurate knowledge about each antibiotics use, mechanism of actions, on which microorganisms it acts, prescribed by them and should continue education about them in their dental practices. Dentists should follow guidelines before prescribing antibiotics to reduce resistance

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