

Dentistry and Antibiotics: A Review

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Abstract

The dentist in the course of everyday practice is frequently called upon to treat a variety of infections which may be caused by viruses, bacteria, and sometimes fungi. The ability to treat these infections successfully has been totally revolutionized since the discovery and subsequent clinical application of certain chemical substances which are produced by the microorganisms and has the ability to suppress or actually kill other microorganisms, these chemical substances are known as antibiotics. Approximately 10% of all antibiotic prescriptions are linked with dental infections and there's a widespread abuse of antibiotics in medical and dental field. The inappropriate use of antibiotics leads to increased treatment costs, increased risk of adverse events associated to the antibiotic used and most significantly development and propagation of antimicrobial resistance. The definitive indications to be used of antibiotics in dentistry are limited and specific. The purpose of this review article is to discuss about the legitimate use of antibiotics in dental practice for control of oral infection, antibiotic prophylaxis in case of systemic conditions and the overuse and misuse of antibiotics.

Keywords: Antibiotics, Dentistry, Infections.

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INTRODUCTION

Dentistry is a comprehensive speciality devoted to resolving dental infections or restoring and rehabilitating tooth structure lost to the bacterial processes [1]. The use of antibiotics is an integral part of dentistry as they are most frequently prescribed medication for the treatment as well as prevention of bacterial infection in modern medicine. The oral cavity is a complex biological ecosystem with very large number of organisms living in a biofilm [2] and antibiotics cure the disease by killing, injuring, or inhibiting the growth of these bacteria at very low concentrations [3]. The word antibiotic came from the word "antibiosis" a term coined in 1889 by Pasteur which suggested a process by which life might be utilized to destroy life. Term antibiotic was initially used by Selman Waksman in 1942 and his collaborators in journal articles to describe any substance produced by a microorganism that is opponent to the growth of other microorganisms in high dilution [4]. Oral infections are classified as odontogenic and non-odontogenic. Odontogenic infections are the far most

frequent and start affecting periodontal and dental structures. Non-odontogenic infections start in extra dental structures like mucosa, glands, tongue, etc. These infections are usually localized and respond well to treatment. However, favored by children's special features, they can spread to remote regions and cause serious problems compromising even the patient's life [5]. Only a few of the microorganisms cause odontogenic infections, in disease state, other non pathogenic bacterial species contribute by making an ecosystem beneficial for growth and survival of the pathogenic species. The onset of disease is due to a shift in microbial flora. Understanding this ecological principle is important while treating oral and dental infections. Micro-organisms in a biofilm are consistently more resistant to usual dosage of antibiotics by 1000-1500 fold [6]. Young children tend to lack medical antecedents suggesting the likelihood of drug allergies or adverse reactions. The greater proportion of water in the tissues of children, and their increased bone sponginess facilitate faster diffusion of infection. Hence they require adequate dose adjustment of the prescribed medication. The deficient oral hygiene

found in most children and the consumption of sugar-rich foods contribute to increase the presence of microorganisms in the mouth and thereby increasing the risk of bacteraemia following oral treatments. As dental practitioners the knowledge on antibiotics and its prescription is important because it plays a crucial role in our day to day clinical practice for the treatment of oral and dental infections [7]. The present study reviews antibiotic use in dental practices, and contributes elements to favor the rational use of such medicines.

History of Antibiotics

Infections were the major cause of death during the nineteenth century. The introduction of antibiotics not only helped in the treatment of infections but also have a major role in decreasing mortality and morbidity. In 1910 Paul Ehrlich developed the first antimicrobial salvarsan for the treatment of syphilis, a disease that was almost incurable back then [8]. In 1932 prontosil, a sulfonamide antibiotic was discovered and since it was cheap, many companies were encouraged to mass produce many derivatives of prontosil [9]. During the second half of the nineteenth century and before the important discovery of Fleming many researchers recorded observations regarding the antibacterial properties of penicillium fungi. Fleming introduced "penicillin" in 1929 as a compound with germicidal properties, when he noticed that a bacterial growth was terminated by a mold, however, because prontosil was available there was not much interest in penicillin. Till 1941, the purity of extracted penicillin was only 0.3 to 7%, which was not sufficient to be clinically used. Dorothy (Crowfoot), Hodgkin and Barbara Low in 1945 used x-ray crystallography to discover the chemical structure of penicillin and in 1950 penicillin was chemically synthesized. The isolation of 6-aminopenicillanic acid in 1958 led to the semisynthesis of new penicillins such as ampicillin, methicillin and carbenicillin [10]. Few years later, ticarcillin (1971) and piperacillin (1977) were synthesized and in 1989 the combination of piperacillin- tazobactam was introduced and was widely used because of its high activity against gram positive bacteria [11].

Choice of an Antibiotic

Many therapeutically effective antimicrobials are now available and more are being added, it is necessary to lay down certain guiding principles for tailoring a rational therapeutic regimen for an individual patient. Choice of an antibiotic is made on the following factors:

- Host related factors: Age, Renal and hepatic function, Local factors
- Pathogen related factors
- Drug factors: Spectrum of activity, Cost consideration, Compliance by the patient [12].

Mode of Action

1. Inhibit synthesis of peptidoglycan. These antibiotics work by causing hindrance in the synthesis of bacterial cell walls by either: blocking the transport of peptidoglycan monomers synthesized in the cytosol across the cytoplasmic membrane, hampering a transpeptidase and hence the formation of the peptide cross-links, or blocking both the transglycosidase and transpeptidase enzymes. The transglycosidases are necessary for the formation of glycosidic bonds between transpeptidases and sugars are essential for the formation of peptide cross-links [13].
2. Alter the microbial cytoplasmic membrane. Polymixins are cationic peptides which consist a cyclic peptide with a fatty acid chain. The interaction between the cationic peptide and the membrane causes disruption of the bacterial cell membrane and increases the permeability of cell components [14].
3. Alter translation. Many antibiotics work by binding to bacterial ribosomes. Examples of antibiotics that work by binding to the 30S ribosomal subunit are aminoglycosides and tetracyclines, which prevent the binding of Trna [15, 16]. Other macrolide antibiotics, such as erythromycin, bind to the 50S ribosomal subunit and block the exit tunnel of the bacterial ribosome [17].
4. Antibiotics inhibit nucleic acid replication by blocking enzymes i.e. topoisomerases which are essential for supercoiling, bacterial DNA replication and separation of circular bacterial DNA. The fluoroquinolone antibiotic class contains potent inhibitors for topoisomerases or DNA gyrase [18].
5. Inhibit transcription. Some antibiotics, such as rifampin or rifampicin, work by binding to RNA polymerase and inhibiting the transcription of DNA to mRNA [19].

Principles of Antibiotic Usage [20-22]

In recent times, antibacterial administration has been given lots of importance both at the patient as well as at the community level. Antimicrobial stewardship (administration) is defined as "the optimal selection, dosage, and duration of antimicrobial treatment which results in the best clinical outcome for the prevention or treatment of infection, with less toxicity to the patient and minimal impact on subsequent resistance." 4 D's of antimicrobial therapy were summarised by Joseph and Rodvold which is given in Table 1. An important consideration in starting antibiotic therapy is to check if the infection is localized and if the patient has an adequate immune response to control the bacteria if supported surgically. These considerations are summarised in Table-2.

In the presence of purulence, signs of inflammation, abscess or draining sinus tracts, the lesion/ infection responds to local debridement measures in a healthy patient. In an otherwise healthy patient, infections that have not crossed the dentoalveolar regions are amenable to treatment without

antibiotics. The infections that breach to the dentoalveolar regions and threaten to spread into deeper hard tissues or into the soft tissue fascial spaces in the head and neck region will need use of appropriate antimicrobial therapy along with surgical therapy.

Table-1: 4 D's of antimicrobial therapy

Right Dose
Right Drug
Right Duration of therapy
De-escalation to pathogen-directed therapy,

Table-2: Indications and contraindications of antimicrobial therapy

Indicated clinical conditions for antimicrobial therapy	Non-indicated clinical conditions for antimicrobial therapy
1. Pyrexia which has lasted for 24 hours – indicates a systemic response to the infection 2. Systemic symptoms like malaise, fatigue, weakness, dizziness, rapid respiration and local tender lymphadenopathy – indicate an impending sepsis 3. Trismus– here antibiotics are indicated because infection can spread to perimandibular spaces and can extend to secondary spaces that can be potentially dangerous. 4. As a prophylaxis in patients with systemic conditions like rheumatic heart disease, endocarditis, heart / orthopaedic prosthesis. 5. In immunocompromise patients – AIDS, cancer, corticosteroid therapy, autoimmune diseases, cyclic neutropenia, pancytopenia, uncontrolled diabetes etc. 6. After solid Organ transplant/grafts (cardiac/renal/bonemarrow/liver/osseous implants)	1. Pain – (Analgesics/ Anti-inflammatory drugs are indicated) 2. Oedema – (Anti-inflammatory drugs indicated) 3. Redness/heat (Anti-inflammatory drugs indicated) 4. Purulence – (Resolved by drainage of pus / debridement) and thus antibiotics are not required. 5. Abscess – localized (e.g., alveolar abscesses, periodontal abscesses) – (Resolves by incision and drainage) 6. Draining sinus tract in which there is removal of foci of infection and sinus tract may heal on its own or may have to be surgically excised.)

Table-3: Antibiotics commonly used in application to odontogenic infections [23]

DRUG SUBSTANCE	ROUTE	DOSAGE	SIDE EFFECTS
Amoxicillin	Oral	500 mg/8 hours 1000 mg/12 hours	Diarrhea, nausea, hypersensitivity reactions
Amoxicillinclavulanic acid	Oral or IV	500-875 mg/8 hours* 2000 mg/12 hours* 1000-2000mg/8 hours**	Diarrhea, nausea, candidiasis, hypersensitivity reactions
Clindamycin	Oral or IV	300 mg/8 hours* 600 mg/8 hours**	Pseudomembranous colitis
Azithromycin	Oral	500 mg/24 hours 3 consecutive days	Gastrointestinal disorders
Ciprofloxacin	Oral	500 mg/12 hours	Gastrointestinal disorders
Metronidazole	Oral	500-750 mg/8 hours	anesthesia/paresthesia of the limbs, Seizure, incompatible with alcohol ingestion
Gentamycin	IM or IV	240 mg/24 hours	Ototoxicity Nephrotoxicity
Penicillin	IM or IV	1.2-2.4 million IU/24 h*** Up to 24 million IU/24 hours**	Hypersensitivity reactions, gastric alterations

*= ORAL ROUTE, **= INTERVENOUS ROUTE and ***=INTERMASCULAR ROUTE OF DRUG ADMINISTRATION.

Table-4: Regimen revised by the American Heart Association (AHA) in 2014 [24]

Regimen: Single Dose 30 to 60 min before procedure			
Specific	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin /Cephtriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to Penicillins or Ampicillin - oral	Cephalexin Or	2g	50 mg/ kg
	Clindamycin Or	600 mg	20 mg/kg
	Azithromycin/Clarithromycin	500 mg	15 mg/kg
Allergic to penicillin or Ampicillin and unable to take oral medication	Cefazolin /Ceftriaxone Or	1 g IM or IV	50 mg/kg IM or IV
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

The Drug Dosage of Mainly Used Antibiotics

Amoxicillin

Amoxicillin is a broad spectrum Penicillin group of antibiotics. It became first available in 1972 and one of the most commonly prescribed antibiotics in children. It is present on the World Health Organization's list of Essential Medicines, the most important medication needed in a basic health system²⁵. It is active against many gram positive and gram negative bacteria e.g. Streptococcus, Bacillus subtilis, Enterococcus, Haemophilus, Helicobacter, and Morexellaetc, whereas Citrobacter, Klebsiella, and Pseudomonas aeruginosa are resistant to it. Some E.coli and most clinical isolates of Staphylococcus aureus have developed resistance to it. Amoxycillin is indicated in Dental prophylaxis in patients at risk of endocarditis, upper respiratory tract infection, treatment of pulpal, periapical and periodontal infection, infection of skin and soft tissues due to streptococci and susceptible staphylococci. It is contraindicated in Penicillin allergy, hypersensitivity reaction (anaphylaxis or Steven Johnson syndrome), kidney disease, phenylketonuria.

Dosage [26]: Child dose: 25-50mg/kg/day q 8-12 hr oral and Adult dose: 250-500 mg q 6-8 hr. Maximum dosage for Children: 2 g/day

Available as: Caps 250 and 500 mg, DT 125 mg, 250 mg, syrup 125 mg/ 5 ml and 250 mg/5ml; drops 100 mg per ml (AMOXIL, AMOCLOX, NOVAMOX, AMOXYBID, COMOXYL, CIDOMEX)

Cephalosporins

Cephalosporins were discovered in 1945 and indicated for the prophylaxis and treatment of infections for children who are allergic to penicillin group of drugs. First generation cephalosporins are active predominantly against gram positive bacteria, and further generations have increased activity against gram negative bacteria.

Cephalexin

Dosage [26]: 25-100 mg/kg/ day q 6-8 hrs oral; Adult dose: 250-500 mg every 6 hours (maximum 4g/day).

Available forms: Tablet 500mg, 1g (CEDADROX, ODOXIL), Capsule 500 mg (IYDROXIL), Oral suspension 125MG/5ML, 250 mg/5 ml and 500 mg/5 ml (DROXYL, IYDROXIL).

Cefixime

Dosage [26]: 8 mg/kg/day oral once or twice a day; Adult dose: 200-400 mg daily q 12-24 hr Available forms: Tablet 50 mg, 100mg, 200mg, 400 mg, and syrup 100 mg/5 ml, 200 mg/5 ml and 500 mg/5 ml.

Doxycycline Hyclate

Dosage [26]: 2-5 mg/kg/day q 12 hr oral; Adult dose: 200 mg on day 1, then 100 mg daily (Avoid in children below 8 years of age due to risk of staining of teeth and growth retardation, pregnancy and lactation) Available forms: 50 mg, 100 mg, 200 mg tabs and syrup 25mg/5ml, 50 mg/5ml (CEDOX DT, REVIDOX, VIVOCYCLINE, DOX-T, MINICYCLINEN, TETRADOX, VIBAZINE DT, SOLOMYCIN; MINOCYCLINE SYRUP)

Available forms: Tablet 125mg, 250 mg and 500mg (SPORIDEX DT, CEFF KID TAB), Capsule 250 mg, 500 mg (CEPHAXIN, SEPEXIN, CEFF, SPORIDEX, MONACEF, SOLEXIN), Oral Suspension

Metronidazole

Metronidazole was introduced in 1959 and is one of the mainstay drugs for the treatment of anaerobic and certain parasitic infection. It is a potent inhibitor of obligate anaerobic bacteria and protozoa. It is indicated in acute necrotizing ulcerative gingivitis, Pericoronitis and pericoronal abscess, Chronic aggressive periodontitis, Periapical and periodontal abscess, Dentalveolar abscess, Cellulitis and Space infections, Osteomyelitis, Infected sockets, Surgical prophylaxis and contraindicated in hypersensitivity to metronidazole and alcohol consumption [27].

Dosage [28]: 30 mg/kg/day in 3 divided doses; Age 1 – 3 years: 150 mg in three divided doses, Age 3 – 7 years: 200 mg in three divided doses, Age 7 - 10 years: 300 mg in three divided doses; Maximum dosage for Children: 2 g/day ; Adult dose: 200-400 mg q 8 hr.

Available forms: Tablet 200 mg, 400 mg, Infusion solution 500 mg/100ml, Oral suspension 200 mg/5 ml (FLAGYL, ARISTOGYL, METROGYL, ROGYL).

Antibiotic Combinations

Antibiotic combinations are used to enhance antibacterial activity against manifold potential pathogens for initial empirical treatment, as it may enhance or impair the overall antimicrobial activity. Drug combinations may have additive/super additive toxicities and the selection of an appropriate combination requires an understanding of the potential for interaction between the antimicrobial agents.

Amoxicillin with clavulanic acid

Amoxicillin/Clavulanic acid combination was introduced in United States in 1984 as an antimicrobial agent that would increase the activity of Amoxicillin by the addition of the beta-lactamase inhibitor Clavulanic acid. It covers the wide spectrum activity with coverage of betalactamase producing strains of S. pneumonia, S.aureus, H.influenza but is contraindicated in jaundice, penicillin allergy, hepatic dysfunction.

Dosage [28]: For Severe infections 45mg/kg/day every 12 hours Or 40 mg/kg/day every 8 hours, For less severe infections 25 mg/kg/day every 12 hours Or 20 mg/kg/day every 8 hours, 50-100 mg/kg/day (amoxicillin base) q 6-8 hr IV; Adult dose: 250-500 mg of amoxicillin orally 3 times a day, 1.2 g q 6-8 hr IV infusion; Maximum dosage: For children < 40 kg, (1000 – 2800) mg Amoxicillin/ 143 - 400 mg.

Available forms: AUGEMNTIN, ADVENT, MOXCLAV, MOXKIND-CV, MEGACLAV, CLAVAM Tablets 375 mg (AMOXICILLIN 250 mg+ 125 mg clavulanate), 625mg (AMOXICILLIN 500mg+ 125 mg clavulanate) and 1000mg(AMOXICILLIN 875 mg+clavulanate), syrup 156mg/5ml (125 mg amoxicillin +31.5 mg clavulanate); augemntin duo, moxclavb.d. andaugpen HS syrup (200mg amoxicillin +28.5 mg clav/5ml); AUGPEN, AUGMENTIN DDS, MOXCLAV DS.

RECOMMENDATIONS [29]

Dental practitioners should be practicing the following general guidelines while prescribing antibiotics for the child patient

- **Pulpitis, acute and chronic apical periodontitis, draining sinus tract, localized intra-oral swelling:** Antibiotic therapy usually is not indicated and nor effective if the dental infection is confined within the pulpal tissue or the immediate surrounding tissue. Therefore, the use of antibiotics should be considered in cases of advanced non-odontogenic bacterial infections such as staphylococcal mucositis, tuberculosis, gonococcal stomatitis, and oral syphilis and in the presence of systemic signs of an infection i.e., fever and facial swelling.
- **Acute facial swelling of dental origin:** Any facial swelling or facial cellulitis secondary to an odontogenic infection with the signs of systemic involvement and septicemia (e.g., fever, malaise, asymmetry, facial swelling, trismus, tachycardia, dysphagia, respiratory distress) warrant emergency treatment. Intravenous antibiotic therapy management is indicated. Derivatives of Penicillin remain the best choice for odontogenic infections; however, additional adjunctive antimicrobial therapy (i.e., metronidazole) can be given where there is anaerobic bacterial involvement. However Cephalosporins can also be considered as another choice against odontogenic infections.
- **Dental trauma:** Systemic antibiotics should be recommended as adjunctive therapy for avulsed immature and mature permanent incisors. Tetracycline (doxycycline twice daily for seven days) is the drug of choice, but child's age must be taken into consideration before the systemic use of tetracycline owed to the risk of discoloration in the developing permanent dentition. Penicillin V or amoxicillin can be given as an alternative in

patients under 12 years of age. The use of topical antibiotics (minocycline or doxycycline) to heighten pulpal revascularization and periodontal healing in immature non-vital traumatized teeth has exhibited some potential. Antibiotics are not indicated for the luxation injuries of primary dentition. Antibiotics can be used in cases of concomitant soft tissue injuries and when imposed by the patient's medical status.

- **Pediatric periodontal diseases:** Patients with aggressive periodontitis require adjunctive antimicrobial therapy in conjunction with treatment. In pediatric periodontal diseases associated with systemic disease (e.g., severe congenital neutropenia, Papillon-Lefèvre syndrome, leukocyte adhesion deficiency), the immune system is unable to control the growth of periodontal pathogens and treatment may involve antibiotic therapy.
- **Endodontic Flare-ups:** Adverse reactions (flare-ups) during the endodontic treatment occur infrequently. Antibiotics are frequently administered to avert the adverse post treatment sequelae of root canal treatment and oral surgery.

Antibiotic Resistance

Antibiotic resistance is considered as one of the biggest threats to global health, food security, and development today. A growing number of infections such as pneumonia and tuberculosis are becoming harder to treat as the antibiotics used to treat them become less competent. Some of the complications associated with the use of antibiotics are drug toxicity, hypersensitivity reactions, antimicrobial drug resistance, superinfection, nutritional deficiencies, masking of an infection. Antibiotic resistance is increased by the overuse and misuse of antibiotics, as well as poor infection prevention and control. According to Dr. Thomas J. Pallasch, antibiotic misuse in dentistry mainly involves prescribing them in 'inappropriate situations' or for too long, which includes [30, 31].

- Giving of an antibiotic after any dental procedure in an otherwise healthy patient to stop spread of infection which in all likelihood will not occur.
- Using antimicrobials as analgesics, mostly in endodontics - employing antibiotics for prophylaxis in patients not at risk for metastatic bacteremia
- Using of an antibiotics for the treatment of chronic adult periodontitis, which is almost totally responsive to mechanical treatment
- Using antibiotics instead of surgical incision and drainage of infections
- Using antibiotics to prevent claims of negligence.

A global action plan on antimicrobial resistance, was countersigned at the World Health Assembly in May 2015 with an aim to ensure

prevention and treatment of infectious diseases with safe and effective medicines. Global action plan on antimicrobial resistance has 5 strategic objectives i.e. To improve awareness and understanding of antimicrobial resistance, To strengthen surveillance and research, To reduce the incidence of infection, To optimize the use of antimicrobial medicines and To ensure sustainable investment in countering antimicrobial resistance [32].

CONCLUSION

Appropriate and correct use of antibiotics is essential to ensure that effective and safe treatment is available. Practices that may enhance microbial resistance should be avoided. To improve standards of care, dentists need to be up-to-date in their knowledge of pharmacology in dental education, as well as in the continuing education, with a continuous assessment of dental practices, a better understanding of the pathogenesis of these infections, including the host immune response to bacteremia, along with prospective clinical trials, which will allow for more evidence-based decisions. Every dental professional must follow proper guidelines given by the American Association of Pediatric dentistry (AAPD) which is based on scientific evidence to use antibiotics conservatively.

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