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Antibiotics and its use in pediatric dentistry: A review

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Abstract
Antibiotics are commonly used in dentistry for prophylactic as well as for therapeutic purposes. Very often antibiotics are used in unwarranted situations, which may give rise to resistant bacterial strains. Good knowledge about the indications of antibiotics is the need of the hour in prescribing antibiotics for dental conditions. The purpose of this review article is to provide information on proper use of antibiotics in pediatric dental practice for control of oral infection, and in the management of children with systemic conditions which may alter disease resistance and healing response.

Keywords: Antibiotics, prophylaxis, infection, children

Introduction
Antibiotics are among the most frequently prescribed medication for the treatment as well as prevention of bacterial infection in modern medicine. Antibiotics cure disease by killing, injuring, or inhibiting the growth of bacteria at very low concentrations. [1] The word antibiotic came from the word "antibiosis" a term coined in 1889 by Louis Pasteur which means a process by which life could be used to destroy life.The term antibiotic was first used in 1942 by Selman Waksman and his collaborators in journal articles to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution. [2]

Infection remains a major problem in medical practice, and their rational treatment with drugs is of prime importance. Infection is a process in which bacteria, viruses, fungi or other organisms enter the body, attach to cells, and multiply. [3] Oral infections are poly-microbial and mixed. They arise when normal flora changes from commensal to opportunistic due to a broken balance with the host in certain circumstances. The oral microbial flora starts to grow in the new born's mouth about eight hours after birth. This is followed by a continuous change in its composition from the time the child is edentulous until teeth appear. [4]

Oral infections are classified as odontogenic and non-odontogenic. Odontogenic infections are the most frequent and begin affecting periodontal and dental structures. Non-odontogenic infections start in extra dental structures, such as 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]

A series of differential characteristics should be explained in relation to antibiotic treatment in children: [6]

- Young children tend to lack medical antecedents suggesting the possibility 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 essential as it plays Plays an important role in our day to day clinical practice for the treatment of oral and dental infections.

History of Antibiotics

Illness has been man's heritage from the beginning of his existence, and the search of remedies to combat it is perhaps equally old. The discovery of Penicillin, one of the world's first antibiotics, marked a true turning point in human history when doctors finally had a tool that could completely cure their patients of deadly infectious diseases. Penicillin was discovered in London in September of 1928 by Alexander Flemming. [7]

German chemist Gerhard Domagk (1895–1964) in 1935 discovered Prontosil, the first Sulfa drug. Streptomycin was first isolated on October 19, 1943, by Albert Schatz, a graduate student, in the laboratory of Selman Abraham Waksman at Rutgers University. Tetracycline was patented in 1955 by Lloyd Conover, which became the most prescribed broad spectrum antibiotic in the United States. SmithKline Beecham patented Amoxicillin or amoxicillin/potassium clavulanate tablets, and first sold the antibiotic in 1998 under the trade names of Amoxicillin, Amoxil, and Trimox. [8]

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.

The choice of an antbiotic depends on the following factors: [9]

A. Host related factors: Age, Renal and hepatic function, Local factors
B. Pathogen related factors
C. Drug factors: Spectrum of activity, Type of activity, Compliance by the patient, Cost consideration

β-lactam Antibiotics

β-lactam antibiotics are useful and frequently prescribed antimicrobial agents that share a common structure and mechanism of action of inhibiting the synthesis of the bacterial peptidoglycan cell wall. β-lactam antibiotics include Penicillins and Cephalosporins. [10]

Amoxicillin

Amoxicillin is an extended spectrum Penicillin group of antibiotics. It became first available in 1972. It is on the World Health Organization's list of Essential Medicines, the most important medication needed in a basic health system. It is one of the most commonly prescribed antibiotics in children.

Amoxicillin is active against many gram positive and gram negative bacteria. In general, Streptococcus, Bacillus subtilis, Enterococcus, Haemophilus, Helicobacter, and Morexella are susceptible to amoxicillin, whereas Citrobacter, Klebsiella, and Pseudomonas aeruginosa are resistant to it. Some E.coli and most clinical isolates of Staphylococcus aureus have developed resistance to Amoxicillin to varying degrees [11].

Therapeutic uses: [12]

- Dental prophylaxis in patients at risk of endocarditis (single dose)
- For the treatment of pulpal, periapical and periodontal infection.
- Upper respiratory tract infection due to Streptococci, Pneumococci and H. influenza
- Infection of skin and soft tissues due to streptococci and susceptible staphylococci.

Contraindication

- Penicillin allergy
- Hypersensitivity reaction (anaphylaxis or Steven Johnson syndrome)
- Kidney disease
- Phenylketonuria
- Intestinal colitis

Pediatric Dosage: [12]

Children up to 10 years > 40 kgs - 125– 250 mg every 8 hours

Children up to 10 years < 40 kgs - 20 – 40 mg/kg daily in divided doses every 8 hours or 25 - 45 mg/kg daily in divided doses every 12 hours

Maximum dosage for Children: 2 g/day

Infants < 3 months old - Maximum of 30 mg/kg daily in divided doses

Available forms: Tablet 125 mg, Capsule 250 mg and 500 mg, Oral suspension 125mg/5ml and 250mg/5ml

Cephalosporins

Cephalosporins were discovered in 1945 by the Italian pharmacologist Giuseppe Brotzu and were first sold in 1964. They are 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 successive generations have increased activity against gram negative bacteria. [7]

Cephalexin

Pediatric Dosage: [12]

25-100 mg/kg/ day every 6-8 hours

Available forms: Tablet 125mg, 250 mg and 500mg, Capsule 250 mg, 500 mg and 750 mg, Oral Suspension 125 mg/5ml and 250 mg/5ml.

Cefadroxil

Pediatric Dosage: [12]

30-40 mg/kg/day in 2 divided doses

Available forms: Tablet 1g, Capsule 500 mg, Oral suspension 250 mg/5 ml and 500 mg/5 ml

Cefixime

Pediatric Dosage: [12]

8 mg/kg/day in 2 divided doses for children weighing <50 kgs or < 12 years.

Available forms: Tablet 400 mg, Chewable Tablet 100 mg and 200 mg and Oral suspension 100 mg/5 ml, 200 mg/5 ml and 500 mg/5 ml.

Nitroimidazole

The history of Nitroimidazole as agents for clinical disease began with the recognition in 1953 that vaginitis was caused by the protozoan Trichomonas vaginalis. This led to the intensive search for a drug that would provide an effective treatment. Among 5-nitroimidazoles, metronidazole, imidazole and ornidazole are in widespread clinical use in dentistry [2].

Metronidazole

Metronidazole was introduced in 1959 and is one of the mainstay drugs for the treatment of anaerobic and certain parasitic infection. Metronidazole is a 5-nitroimidazole available for oral administration or as a suppository; also formulated as hydrochloride for intravenous use, and as a benzoate in an oral suspension and also a dental gel.

It is a potent inhibitor of obligate anaerobic bacteria and protozoa, but not of any organism that is aerobic or incapable of anaerobic metabolism. [11]

Therapeutic Uses: [12]

- Acute necrotizing ulcerative gingivitis (Vincent's Stomatitis)
- Pericoronitis and pericoronal abscess
- Chronic aggressive periodontitis
- Periapical and periodontal abscess
- Dent alveolar abscess
- Cellulitis and Space infections
- Osteomyelitis
- Infected sockets
- Gastro-duodenal ulcers caused by Helicobacter pylori
- Surgical prophylaxis

Contraindications:

Hypersensitivity to metronidazole and alcohol consumption.

Pediatric Dosage: [12]

30 mg/kg/day in 3 divided doses

Age 7 - 10 years: 300 mg in three divided doses

Age 3 – 7 years: 200 mg in three divided doses

Age 1 – 3 years: 150 mg in three divided doses

Maximum dosage for Children: 2 g/day

Available forms: Tablet 200 mg, 250 mg, 400 mg and 500 mg, Infusion solution 500 mg/5ml,

Oral suspension 200 mg/5 ml

Antibiotic Combinations

Antibiotic combinations have long been used to provide antibacterial activity against multiple potential pathogens for initial empirical treatment for critically ill patients. The simultaneous use of two or more antimicrobial agents is recommended in specifically defined situations based on pharmacological rationale. However, selection of an appropriate combination requires an understanding of the potential for interaction between the antimicrobial agents. Antimicrobial agents acting at different targets may enhance or impair the overall antimicrobial activity. A combination of drugs also may have additive or super additive toxicities. [13]

Amoxicillin and clavulanic acid

Amoxicillin/Clavulanic acid combination was introduced in United States in 1984 as an antimicrobial agent that would enhance the activity of Amoxicillin by the addition of the beta-lactamase inhibitor Clavulanic acid. During the past 30 years this combination is being used for a variety of pediatric infectious diseases. [14] Amoxicillin and Clavulanate potassium is an oral antibacterial combination consisting of the semisynthetic antibiotic Amoxicillin and Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a β-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid mediated β-lactamases frequently responsible for transferred drug resistance to Penicillins and Cephalosporins. [11]

Pediatric Dosage: [12]

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

Maximum dosage: For children < 40 kg, 1000 - 2800 mg Amoxicillin/ 143 - 400 mg Clavulanic acid

Available forms: Tablet 375 mg, 625 mg and 1000mg, Oral suspension 228.5 mg/5 ml

Role of triple antibiotic paste in reducing dental infections

The infection of the root canal system is considered to be a polymicrobial infection, consisting of both aerobic and anaerobic bacteria. Because of the complexity of the root canal infection, it is unlikely that any single antibiotic could result in effective sterilization of the canal. More likely, a combination would be needed to address the diverse flora encountered. The combination that appears to be most promising consists of Metronidazole, Ciprofloxacin, and Minocycline. This triple antibiotic regimen was first tested by *Sato et al.* in 1996. [15]

In recent years, the Cariology Research Unit of the Niigata University has developed the concept of "Lesion sterilization and tissue repair LSTR" therapy that employs the use of a combination of antibacterial drugs, Metronidazole 500 mg, Ciprofloxacin 200 mg, and Minocycline 100 mg (3 mix used in1:1:1 ratio) for the disinfection of oral infectious lesions, including dentinal, pulpal, and periradicular lesions. A carrier of equal amounts of macrogol ointment and propylene glycol (MP) are mixed together resulting in an opaque mix (MP used in a 1:1 ratio). Either a 1:5 MP: 3mix (creamy consistency) or 1:7 MP: 3mix (standard mix) can be prepared. The antibiotic paste is left in the tooth for a period of 4 weeks to allow complete disinfection of any necrotic tissue. After this period the tooth is re-entered for further treatment. [16]

Use of Triple antibiotic paste [16]

A) Regenerative endodontic treatments
B) In healing of large periradicular lesions
C) Killing common endodontic pathogens from necrotic/infected root canals *in vitro*.
D) In order to sterilize the infected root dentine, especially the deep layers
E) Traumatized immature tooth with a periapical lesion.

Antibiotic combinations in Pediatric restorative dentistry

Pediatric restorative dentistry has evolved and got revolutionized over the years. The search for an ideal restorative material has led the researchers for the development of numerous restorative materials each surpassing the other with their innumerable advantages over one another. [17]

The addition of antibiotics to Glass ionomer cement (GIC) has recently been recommended for the treatment of carious lesions aiming to reduce the total number of viable bacteria, while preserving dentin tissue and pulpal vitality. A combination of Ciprofloxacin, Metronidazole and Minocycline has been showed to be successful in sterilizing carious lesion samples. Staining of dentin, however has been reported with the use of Minocycline in the antibiotic mixture. Therefore, variations of the original triple antibiotic mixture has been suggested, whereby Minocycline was left out of the combination (i.e) Bi antibiotic paste containing Metronidazole and Ciprofloxacin has been suggested. Amoxicillin has been used both systemically and locally in the treatment of various infectious diseases. In addition the combination of amoxicillin and metronidazole is the most prescribed antibiotic combination in dentistry. [18]

Antibiotic Prophylaxis

Most oro-facial infections are odontogenic in origin, and are of self-limiting nature characterized by spontaneous drainage.

The causal bacteria are generally saprophytes. Bacteremia is anticipated in the blood following invasive dental procedures. Infective endocarditis (IE) is an uncommon but a life-threatening complication resulting from bacteremia [19].
The vast majority of cases of IE caused by oral microflora can result from bacteremia associated with routine daily activities such as tooth brushing, flossing and chewing. However, antibiotic prophylaxis is recommended with certain dental procedures.

Recommendations: [20]
The conservative use of antibiotics is indicated to minimize the risk of developing resistance to current antibiotic regimen. Antibiotic prophylaxis is given prior to dental procedures in children having the following conditions.

- Patients with cardiac conditions
- Patients with compromised immunity
- Patients with shunts, indwelling vascular catheters, or medical devices
- Patients with prosthetic joints

The procedures which require and do not require antibiotic prophylaxis are given in Table 1
The specific antibiotic regimen revised by the American Heart Association (AHA) in 2014 is given in Table 2

Problems arising while using antibiotics
Antibiotics are prescribed for oral conditions related to endodontic, oral surgical and periodontal manifestation. [21] Unwarranted use of antibiotics are reported in children; mostly for ear and dental infections. However, in children increasing microbial resistance to antibiotics is well documented and is a serious global health concern. Antibiotic resistance is due to inappropriate use of antibiotics by clinicians. According to Dr. Thomas J. Pallasch, antibiotic misuse in dentistry mainly involves prescribing them in 'inappropriate situations' or for too long, which includes, [22]

- Giving an antibiotic after a dental procedure in an otherwise healthy patient to 'prevent' infection which in all likelihood will not occur.
- Using antibiotics as analgesics, particularly in endodontics - employing antibiotics for prophylaxis in patients not at risk for metastatic bacteremia
- Using antimicrobials to treat 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

The impression is that antibiotics continue to be prescribed by dentists as much or more as in the past, despite the scarcity of clinical trials demonstrating the need for antibiotics.
Some of the problems associated with the use of antibiotics are drug toxicity, hypersensitivity reactions, antimicrobial drug resistance, superinfection, nutritional deficiencies, masking of an infection.

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.

Table 1: Procedures requiring and not requiring Antibiotic Prophylaxis [19]

Dental procedures requiring antibiotic prophylaxis
Dental extractions
Periodontal procedures including surgery, scaling, root planing and probing
Dental implant placement, reimplantation of teeth
Endodontic instrumentation or surgery beyond the tooth apex
Subgingival placement of antibiotic fibers or strips
Initial placement of orthodontic bands but not brackets
Intra-ligamentary local anaesthetic injections
Prophylactic cleaning of teeth or implants with anticipated bleeding
Dental procedures not requiring antibiotic prophylaxis
Routine anaesthetic injections through non-infected tissue
Taking dental radiographs
Taking oral impressions
Placement of removable prosthodontic or orthodontic appliances
Adjustment of orthodontic appliances, placement of orthodontic brackets
Restorative procedures with or without retraction cord
Placement of Rubber dam
Shedding of deciduous teeth
Bleeding from trauma to the lips or oral mucosa
Post-operative suture removal
Fluoride application

Table 2: Specific antibiotic regimen revised by the American Heart Association (AHA) in 2014 [20]

Regimen: Single Dose 30 to 60 min before procedure			
Situation	**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 /Cephtrioxone	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 /Ceftrioxone Or	1 g IM or IV	50 mg/kg IM or IV
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

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