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CLINICAL APPLICATION OF ANTIBIOTICS FOR THE MANAGEMENT OF PERIODONTAL DISEASE, A SYSTEMATIC REVIEW

Ali Forouzanfar

Research Center for Patient Safety, Mashhad University of medical sciences, Mashhad, Iran.
IRAN Oral & Maxillofacial Diseases Research Center, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran.

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ABSTRACT

Periodontal diseases are inflammatory conditions that affect the soft and hard tissues supporting the teeth. It is well understood that various forms of periodontal diseases and tooth caries are caused by several bacteria existing in an organized structure called dental plaque. Considering the bacterial etiology of periodontal disease, this article represents a systematic review for the role of antibiotics in treatment of periodontal infections based on Medline search strategy.

INTRODUCTION

The most frequent infectious conditions in humans are probably dental caries and periodontal diseases that result from actions of dental plaque. This bacterial plaque is a yellowish biofilm forms on the teeth surfaces and contains communities of disease-causing bacteria, microorganisms such as fungi, food debris, and salivary products. Recent studies have revealed that about 500 different bacterial species have the ability to colonize the mouth and any individual may have at least 150 or more different species. Growth and maturation of disease-causing bacteria especially gram negative anaerobes that are responsible for gingival and periodontal diseases occur if the plaque remains on the tooth surface for several hours [1-5].

The primary colonizing bacteria that are usually present at the mouth adhere to the tooth surface and if not clean regularly, attach to the secondary bacterial colonizers by providing special receptors. This process of attachment is called Coadhesion or Co-aggregation that leads to the development of microcolonies and ultimately to a mature biofilm. A complex mature biofilm protect the bacteria from the host's immunologic mechanisms as well as from chemical mouth rinse and antibiotics used for treatment of the disease. An antibiotic strength interestingly should be 500 times greater than the usual therapeutic dose for affecting the bacteria that have arranged in dental plaque. With the passage of time in the subgingival plaque there would be also a progressive shift from gram-positive facultative bacteria to gram-negative, anaerobic species. These pathogens include, but are not limited to *Treponema*, *Bacteroides*, *Porphyromonas*, *Prevotella*, *Capnocytophaga*, *Peptostreptococcus*, *Fusobacterium*, *Actinobacillus*, and *Eikenella*[6-10]. Table 1 shows the main species of bacteria known as the first or secondary colonizers.

Corresponding Author

Ali Forouzanfar
Email: Ali.forouzanfar@gmail.com

The periodontal pathogen species possess a number of virulence factors, including endotoxin, leukotoxin, collagenase, and protease for triggering the host cells to produce pro-inflammatory cytokines and other chemical mediators of inflammation. Cytokines are soluble proteins, produced by host cells, which regulate cellular interactions with signal messaging. Their actions are regulation of growth, differentiation, initiation and maintenance of immune and inflammatory responses. One of the most important cytokine groups are interleukins that are involved in communication between leukocytes and other cells, such as epithelial, endothelial and fibroblasts for conducting immune and inflammatory processes [11-14].

Periodontal infection in the early stages is called gingivitis and if untreated turns to periodontitis at the later stages. Gingivitis determines by gum swollen, redness and bleeding which is the immune's natural response to the presence of destructive bacteria around the tooth. The advanced form of periodontal disease is called periodontitis which is diagnosed by inflammatory gum attachment loss, alveolar bone break down and finally tooth mobility [15-17]. Table 2 presents classification of periodontal disease conditions and their diagnostic criteria.

Antibiotics in periodontal treatment

An antibiotic is a natural or synthetic agent that kills or inhibits the growth of selective microorganisms, usually at low concentrations. They are indicated for treatment of advanced and aggressive forms of periodontitis, prophylaxis of cardiovascular high-risk individuals, major implant or bone graft surgeries and before periodontal procedures of immune-compromised patients. In periodontal treatment antibiotics are administered *locally* or *orally* for reducing the number of bacteria present in the diseased tissues. Since the bacteria can invade periodontal tissues and mechanical therapy like scaling and root planning would be ineffective, the *systemic administration* of antibiotics may be a necessary adjunct for the controlling of bacterial infection. The *local administration* directly to the periodontal pocket provides greater concentrations of antibiotics to the infected area and reduces the side effects of systemic administration. The main criteria of selecting an antibiotic in periodontal medicine are sensitive and specific for periodontal pathogens, not allergenic, nontoxic, substantive, not routine, and inexpensive. Although oral bacteria are susceptible to many antibiotics, but the concentration of a single agent decrease in the gingival fluids and all putative periodontal pathogens cannot be inhibited. For this reason a combination of two antibiotics and using an antiseptic mouth rinse may be recommended to get rid of all involved pathogens of periodontal tissues. Table 3 shows some examples of routine antibiotics for single versus combination therapy. They should be prescribed due to the manufacturer's guidelines for warnings, contraindications, and precautions of use [18-23].

Amoxicillin

Amoxicillin is a semi-synthetic penicillin antibiotic that has been used since 1972 and is one of the most commonly prescribed antibiotics in children and adults with an extended anti-infective spectrum that includes gram-positive and gram-negative bacteria. Amoxicillin is used in the treatment of several infections, including ear, nose, throat, urinary tract, lung, skin and oral infections. It is also used for prophylaxis to prevent bacterial endocarditis in high-risk individuals before dental treatments such as tooth extractions, all oral surgeries, scaling and root planning. High-risk people include artificial heart valves, major and congenital heart defects and a history of previous endocarditis [24, 25].

In general use, due to the severity and extension of the disease, it may be used alone or together with another antibiotic called combination therapy. In periodontal practice amoxicillin may be useful for the management of patients with localized and generalized aggressive periodontitis and advanced forms of other periodontitis. The recommended dosage is 500 mg three times daily for at least 7 days [26, 27].

Azithromycin

Azithromycine is one of the macrolide antibiotics used for periodontal treatment. Other macrolides used for periodontal treatment include erythromycin and spiramycin which are not in general use. Macrolides inhibit protein synthesis and can be bacteriostatic or bactericidal depending on the concentration of the antibiotic. Azithromycin is effective against gram-negative and anaerobic bacteria and has a significant level of concentration in periodontal tissues after an oral dosage of 500 mg four times daily for 3 days, which is recommended for treating periodontal abscess. It also has the ability to penetrate fibroblasts and phagocytes and transported to the inflammatory sites by phagocytes and released during phagocytosis, therefore azithromycin is suggested to be an effective adjunctive therapy for improving periodontal status in patients with advanced periodontitis [28, 29].

Ciprofloxacin

Ciprofloxacin is a member of fluoroquinolones family, a group of broad-spectrum antibiotics that affects both gram-negative and gram-positive bacteria and plays an important role in treatment of bacterial periodontal infections. Recent studies have revealed that all strains of *A. actinomycetemcomitans*, which is an important periodontal pathogen,are susceptible to ciprofloxacin. It is usually used as a single or combined regimen for controlling severe forms of periodontitis and establishing the periodontal health microflora such as *streptococcus* species [30].

Clindamycin

Clindamycin that is chemically structured as methyl 7-chloro-6,7,8-trideoxy-6-{[(4*R*)-1-methyl-4-

propyl-L-prolyl]amino}-1-thio-L-threo-α-D-galacto-octopyranoside is an effective antibiotic against both aerobic gram-positive cocci and anaerobic, gram-negative rod-shaped bacteria. In periodontal practice clindamycine is used for two purposes, first the situations in which the patient is allergic to penicillins like amoxicillin or ampicillin and second for treating refractory periodontitis and peri-implantitis because of high affinity of clindamycine for osseous tissue. However, it should be noticed that this antibiotic is not usually the first choice of treatment in oral and periodontal disease [31, 32].

Tetracyclines

Tetracyclines are semi-synthetic derivatives of polycyclic naphthacenecarboxamide that have four hydrocarbon rings. These broad-spectrum bacteriostatic antibiotics have been used since 1940 for the treatment of infections of the oral cavity, skin, urinary tract, respiratory tract, and the intestines. This group of antibiotics includes tetracycline, oxytetracycline, doxycycline and minocycline. Tetracyclines have the ability to concentrate in the periodontal tissues and inhibit the growth of *aggregatibacteractinomycetemcomitans,* so they are useful in the treatment of *localized aggressive periodontitis* and other advanced forms of periodontitis. Anticollagenase activity of tetracyclines is of great interest because can inhibit tissue destruction and may promote bone regeneration. Another special distinctiveness of this antibiotic is it's concentration in the gingival crevice that is 2 to 10 times more than the serum levels, that's why tetracycline is effective for the treatment of periodontal diseases. Long-term use of 20 mg of doxycycline twice daily is recommended as a part of sub-antimicrobial dose strategy to inhibit collagenase activity and improving periodontal status [34, 35].

Metronidazole

Metronidazole is a nitroimidazole bactericidal compound that prevents bacterial DNA synthesis and is effective against anaerobes such as *Porphyromonasgingivalis*and *Prevotellaintermedia*, *Fusobacterium*and *Peptostreptococcus* species. This antibiotic is not usually used alone or as the first choice of treatment for *periodontal* infections. Several studies have demonstrated the efficacy of metronidazole for treatment of gingivitis and periodontitis when used in combination with amoxicillin or Ciprofloxacin. When prescribed systemically, metronidazole reduces the growth of anaerobic flora, including spirochetes, and it decreases the clinical signs of periodontitis like bleeding with probing [36, 38].

Table 1. Overview of Primary and Secondary Colonizers in Dental Plaque

Primary colonizers	Secondary colonizers
Streptococcus gordonii, intermedius, mitis, oralis, sanguinis,	*Campylobacter gracilis, rectus, showae*
Actinomycesisraelii, naeslundii, oris,	*Fusobacteriumnucleatumsppnucleatum, vincentii, polymorphum, periodonticum*
Aggregatibacteractinomycetemcomitans serotype a	*Prevotellaintermedia, loescheii, nigrescens*
Capnocytophagagingivalis, ochracea, sputigena	*Streptococcus constellatus*
Eikenellacorrodens	*Tannerella forsythia*
Actinomycesodontolyticus	*Porphyromonasgingivalis*
Veillonellaparvula	*Treponemadenticola*
	Aggregatibacteractinomycetemcomitans serotype b

Table 2. Classification of periodontal disease conditions

Diagnosis considering stage of the disease	Clinical appearance	Diagnostic criteria
Gingivitis	Gingival erythema, Bleeding on probing, Changes in color, size, texture and shape.	The sulcus depth usually remains at levels of 1-3 mm with no attachment loss.
Mild-moderate periodontitis	Gingivitis when the attachment loss has occurred is termed periodontitis. Bone loss and recession usually is seen.	Clinical attachment loss <6mm, Radiographic findings of angular or horizontal bone loss.
Advanced periodontitis	If the attachment loss exceeds 5 mm, the diagnosis would be advanced periodontitis. This form of periodontitis in multi-rooted teeth causes furcation involvement.	Tooth mobility, angular as well as horizontal alveolar bone loss is included in this diagnosis. Furcation involvement is demonstrated by penetrating a periodontal probe through the inter-radicular portion of the tooth.

Table 3. Single Antibiotic Regimens Used to Treat Periodontal Diseases

	Regimen	Dosage/Duration
Amoxicillin	500 mg	Three times daily for 8 days
Azithromycin	500 mg	Once daily for 4 to 7 days
Ciprofloxacin	500 mg	Twice daily for 8 days
Clindamycin	300 mg	Three times daily 10 days
Tetracyclines(Doxycycline/minocycline)	100 mg to 200 mg	Once daily for 21 days
Metronidazole	500	Three times daily for 8 days

Table 4. Combined Conventional Antibiotic Regimens for Treatment of Periodontal Diseases

	Regimen	Dosage/Duration
Metronidazole +Amoxicillin	250 mg of each	Three times daily for 8 days
Metronidazole +Ciprofloxacin	500 mg of each	Twice daily for 8 days

Table 5. Adverse effects of antibiotics used in the treatment of periodontal diseases. In these situations the patient should consult the physician and stop using the medication.

Antibiotic	Most common side effects
Penicillin	Hypersensitivity, rashes, nausea, diarrhea
Azithromycin	Diarrhea, nausea , abdominal pain , and vomiting
Ciprofloxacin	Nausea, diarrhea, abnormal liver function tests, vomiting, and rash
Clindamycin	rashes, nausea, diarrhea
Tetracycline	Gastrointestinal intolerance, Candidiasis, dental staining and hypoplasia in childhood, nausea, diarrhea, interaction with oral contraceptives
Metronidazole	Gastrointestinal intolerance, nausea, antabus effect, diarrhea, unpleasantmetallic taste

CONCLUSION

This article reviewed several antibiotics used for treatment of periodontal diseases, their indications and side effects. Although oral hygiene instruction against dental plaque formation and mechanical periodontal treatment like scaling and root planning improves clinical conditions in most cases, adjunctive antimicrobial agents, used either locally or systemically, is necessary in advanced situations. Since the antibiotic resistance is a global public health problem, care should be taken for selecting the effective antibiotic in any especial condition and preventing the overuse.

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DECLARATION OF INTEREST

The author confirms that this article content has no conflict of interest.

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