ISSN No:-2456-2165

Role of Antimcrobial Agents in Periodontal Therapy- A Review on Prevailing TreatmentModalities

[1.] Dr. Uma Sudhakar, Prof & HOD,
Dept of Periodontology,
Thai Moogambigai Dental College andHospital,
Chennai, India.

[2.] Dr.Snophia Suresh, Professor,
Dept of Periodontology,
Thai Moogambigai Dental College and Hospital,
Chennai, India.

[3.] Dr. Tamannabasha, Junior Resident,
Dept of periodontology,
Thai Moogambigai Dental College and Hospital,
Chennai, India.

[4.] Dr. Ekambareswaran, Junior Resident,
Dept of Periodontology,
Thai Moogambigai Dental College and Hospital,
Chennai, India.

[5.] Dr. Mahesh Kumar, Junior Resident,
Dept of Periodontology,
Thai Moogambigai Dental College and Hospital,
Chennai, India.

Abstract:- Periodontitis, a common inflammatory condition associated with progressive damage of supporting structures of the teeth caused by the host-tissue reaction to the pathogenic bacterial colonies and also by the endotoxins produced by the bacteria. Most likely, higher concentration of microbial colonization in the sub-gingival plaque produces gingivitis and specific forms of chronic periodontitis (non-specific plaque hypothesis). Similarly, specific microbial colonization triggers aggressive periodontal diseases because of their extremely high virulence (specific plaque hypothesis). However, the particular mechanisms by which periodontal supporting tissues are damaged still remains indefinite. Hence the present review was aimed to give a brief knowledge and rationale about the role of antibiotics in periodontal disease.A structured literature search for articles written in the English language in PubMed, MEDLINE, Embase, Google Scholar and Web of Science databases from 1980 to till date was retrieved by using MeSH terms "periodontal therapy", "antibiotics and periodontitis", "Management of periodontitis", "oral and systemic antibiotics" "Periodontal Complications" "antimicrobial oral therapy", "systemic antibiotics and Periodontal treatment" and "prognosis in periodontitis". Systemic antibiotics therapy usually comprise of mono-therapeutic agents like β- lactams antibiotics (amoxicillin, combined with clavulanic acid), metronidazole, tetracycline's (tetracycline, doxycycline, minocycline etc.), clindamycin and quinolones (ofloxacin, ciprofloxacin). Local antimicrobial therapies are specifically recommended for residual pockets or at site where mechanical management becomes difficult to regulate the repeated progression of a microbiota noxious to supportive tissue health.A successful antimicrobial therapy is effectively influenced by the host-immune response, periodontal status of the patient, the microbial ecology of the entire oro-pharyngeal cavity and various local and systemically associated risk factors.One should always remember that antibiotics should be used only as a conjunction with mechanical instrumentation rather than primary treatment option since an inappropriate use will ultimately result in existence of resistance and incompetence. Thus proper, optimal, effective and cautious use of systemic or local antibiotics is highly critical specifically during the course of periodontal disease management.

Keywords:- *Antibacterial Therapy, Aggressive Periodontics, Atridox, Atrisite, Metronidazole.*

I. INTRODUCTION

Dental plaque, calculus and oral biofilm associated with pathogenic microorganisms are often considered as the primary etiological agent for gingivitis and periodontal diseases [1]. Gingivitis is the most prevalent reversible inflammatory condition characterized by swelling and localized bleeding of the gingival soft tissue that often progress into periodontitis with further destruction of underlying periodontal ligament tissue and supporting alveolar bone if left untreated. Thus, periodontitis is defined as an inflammatory condition associated with progressive damage of supporting structures of the teeth caused by the host response to the pathogenic bacterial colonies and also by the endotoxins produced by the bacteria [2]. Numerous studies have also shown microorganisms that contact the tooth often reside on the surface and form atypical matured biofilm structure with compromised vulnerability to antimicrobials. Due to these characteristics of dental biofilm the recommended management of periodontitis includes adequate oral hygiene counseling, creating awareness about the role of diet, oral hygiene practices such as proper tooth brushing, flossing accompanied by skilled cleaning of the

ISSN No:-2456-2165

teeth and gingiva to disorganize the biofilm mechanically using hand instruments or ultrasonic devices before, or soon after the beginning of local or systemic antimicrobial therapy [3].

Most likely, higher concentration of microbial colonization in the sub-gingival plaque initiates gingivitis and certainforms of chronic periodontitis (non-specific plaque hypothesis) similarly specific microorganisms triggers aggressive periodontal diseases because of their extremely high virulence (specific plaque hypothesis) [4]. Some of the notable periodontal pathogens are A.actinomycetemcomitans, P.gingivalis,Prevotella, F. nucleatum and indefinite Enterobacteriaceae species and staphylococci[5].It is evident that microorganisms existing in the periodontal pockets are accountable for these inflammatory changes, but ambiguitystill prevails regarding the particular mechanisms by which periodontal tissues are compromised or damaged. Hence the present review was aimed to give a brief knowledge and rationale about the role of antibiotics in periodontal disease.

II. METHODOLOGY

A structured literature search for articles written in the English language in PubMed, MEDLINE, Embase, Google Scholar and Web of Science databases from 1980 to till date was retrieved by using MeSH terms “periodontal therapy”, “antibiotics and periodontitis”, “Management of periodontitis”, “oral and systemic antibiotics” ”Periodontal Complications” “antimicrobial oral therapy”, “systemic antibiotics and Periodontal treatment” and “prognosis in periodontitis”.

III. ANTIMICROBIAL THERAPY

A successful antimicrobial therapy is influenced by the host-immune response, patient’s periodontal status and microbial ecology of the oro-pharyngeal cavity and various local and systemically associated risk factors [6]. Simultaneously, efficacy of periodontal antibiotic response is influenced by wide spectrum of antimicrobial agents and by pharmacokinetic characteristics of the medication as well as the local environmental factors like drug-tissue binding capacity, non-specific degradation of the drug by floral microorganisms, nature of the sub-gingival plaque biofilm, bacterial load, maximum antibiotic concentration (MAC), effectiveness of the host defense, pathogenic microbial colonization in periodontal tissues, surface of the root and extra-oral resistant sites to antibiotic therapy[7]. These unique therapeutic difficulties imposed by biofilms varyas a result of divergent pathological situations such as chronic periodontitis, Aggressive periodontitis, Necrotizing periodontal disease and periodontal abscess.Herrera et al. (2002) established that in specific clinical circumstances, such as patients with deep pockets, withadvanced or ‘‘aggressive’’ “active” disease, or with specific microbiological colonization, antimicrobial therapy adjunctive to scaling and root planing (SRP) could prove to be clinically significant [8].

Currently, various local and systemic antibiotics have been used for the management of chronic and aggressive periodontal diseases. In clinical situations where conventional treatment becomes ineffective, supplementary and further aggressive treatment is needed. It is evident that specific bacterial species causes periodontal destruction and systemic drug delivery helps to achieve bactericidal or bacteriostatic concentrations of the antimicrobial substance against specific microbes in the periodontal pocket, the furcation area, or at the bottom of a deep periodontal pocket, in the epithelial or connective tissue of the gingiva, or even bacteria colonizing oral mucosa and associated surfaces.If after scaling and root planning or scaling and root planning with controlled systemic antibiotic regimens did not react as required then controlled local delivery of antimicrobials may be applicableto an extent [9].

IV. ROLE OF SYSTEMIC ANTIBIOTICS

Systemic antibiotics therapy usually comprise of mono-therapy based on the β- lactams antibiotics (amoxicillin with or without clavulanic acid), metronidazole, tetracycline’s (tetracycline, doxycycline and minocycline), clindamycin and quinolones (ofloxacin, ciprofloxacin). The antibiotics enter the periodontal pocket or furcation areas through hematogenous route and can disruptthe periodontal pathogenic microorganisms beyond the action point of mechanical instruments or topical antiseptics and chemotherapeutics. These antibiotics have also aided in suppressing periodontal pathogens residing on the tongue and intra-oral surfaces, thereby regressing sub-gingival colonization of pathogens. Antibiotics in the lesser cost group include tetracyclines, amoxicillin and metronidazole. Antibiotics in the greater cost group include azithromycin, clarithromycin, ciprofloxacin, amoxicillin with or without clavulanic acid and clindamycin. In the recent studies, double or triple combination of drugs hasrevealed significant improvement in the prognosis [10].

A) Tetracycline:

Tetracycline was the first evident and effective antibiotics implemented for treatment of periodontitis specifically against gram positive than gram negative microbes. It is frequently used for patients with juvenile onset periodontitis, aggressive periodontitis and in host modulation therapy. These are bacteriostatic agents that suppress A. actinomycetemcomitans predominantly seen in periodontal pockets because of their increased concentration in the gingival crevice (2-10 times) than in blood/serum. About 250 mg of tetracycline is recommended at four times daily for 2 weeks for a normal adult however it is contraindicated in pregnancy. Magnusson et al in his study observed a 2mm (approximately) increase in clinical attachment level (CAL) at the active disease site three months post-operatively and an average decrease of 2.5 mm probing pocket depth is evident 6 months post therapy [11]. Minocyclines are effective against tetracycline-sensitive broadspectrum microbes. It inhibits anaerobic microbes, spirochetes and motile bacteria when used in dosage of 200mg per day over a period of one week. Doxycycline

represents a similar spectrum of activity as minocycline when used in dosage of 100 mg twice daily on the initial stages subsequently by 100 mg once daily. Vyaz et al in a study estimated the efficacy of doxycycline as adjunct to scaling and root planing in treatment of chronic periodontitis showed Doxycycline showed better results after mechanical therapy in the treatment of patients with chronic periodontitis because of its anti-collagenase effect that can inhibit tissue destruction and facilitate bone regeneration [12].

B) Metronidazole:

Metronidazole, a 5- nitro-imidazole substance specifically targets anaerobic microorganisms howeverdoes not show any significant activity against aerobic microbes and micro-aerophilic bacteria. Toxicmetabolites of metronidazole interact with the bacterial DNA and other macromolecular components directly, thus bringing about effective cell lysis (death). It effectively crosses placental barrier and enter fetal circulatory system, similarly it is also secreted in breast milk hence contraindicated in pregnancy. Losche et al in his experimental study on adult periodontitis illustrated that metronidazole along with mechanical debridement by scaling and root planing (SRP) declines the number of teeth requiring periodontal surgery or extraction due to periodontal disease [13].

C) β- lactams antibiotics:

Beta-lactam antibiotics include Penicillin, amoxicillin and cephalosporins. Penicillin though not used in periodontal therapy, acts by suppressing bacterial cell wall production. Amoxicillin is the most common semisynthetic penicillin with broad spectrum activity against both gram positive and negative microorganism widely used in aggressive periodontitis and abscess of the periodontal tissues.The recommended dosage ranges at 500mgthree times a day over a period of 8-10days. Few studies have shown that combination of amoxicillin (a broader spectrumpenicillins) and metronidazole (a nitroimidazoleanaerobic antibiotic) especially in a regime of 500 mg (amoxicillin) and 400mg (Metronidazole) thrice a day for a period of 1 to 2 weeks respectively implies a significant synergistic role in treating anaerobic oral cavity infections and may effectively improve the immediate results of non-surgical therapy in aggressive periodontitis patients thus reducing the need for complex surgical management [14].

Collins et al observed that systemic intake of amoxicillin with clavulanic acid, along with sub-gingival irrigation by antiseptic povidone-iodine improved clinical probing attachment level of about 1 mm in 41% of deep periodontal pocket regions at 3 years post-treatment follow up. These studies also demonstrated that synergistic and combined mechano-therapeutic intervention reduced sub-gingival colonization of P. gingivalis to below evident levels [15].Tenebaumet al in his experimental study illustrated that amoxicillin and clavulanic acid in the gingival crevicular fluid (GCF) well above the minimal inhibitory concentrations (MIC) is effective against certain pathogenic periodontal bacteria after multi-drug therapy [16]. Winkelet al. disclosed that mixture of metronidazole –amoxicillin therapy significantly reduced periodontal pocket depth by inhibiting AggregatibacterActinomycetemcomitansand PorphyromonasGingivalis in chronic periodontitis patients [17].

D) Ciprofloxacin:

Ciprofloxacin is a bactericidal antibiotic of quinolone family acts by cellular lysis and inhibition of DNA replication. Generally, ciprofloxacin like other quinolones (ofloxacin) is well tolerated with insignificant side effects like headache, vomiting sensation, and gastrointestinal pain or discomfort. Ciprofloxacin like tetracycline cross placental barrier and excreted in human breast milk is absolutely contraindicated during lactation and pregnancy.Very few studies have demonstrated adjunctive use of metronidazole with ciprofloxacin in periodontal therapy yet inconclusive [18].

E) Cephalosporins:

Cephalosporins have analogousconfiguration and mechanism as that of penicillin group of drugs. Routinely these drugs are not recommended in treatment of oral-associated infections since penicillins are far responsive to cephalosporins in their wide-range of potential action against periodontal pathogenic bacteria [19].

F) Azithromycin:

Azithromicin, a macrolide antimicrobial agent is effective against anaerobes and gram negative bacilli. It has been suggested that azithromycin as an adjuvant to the treatment of aggressive periodontitis acts by penetrating fibroblasts and induced phagocytes in concentration 100–200 times greater than that of extracellular components. It is widely used in concentration of 500 mg once a day over a period of 3 days or sometimes as single dose of 250 mg after 500mg initial loading dose [20].

V. ROLE OF TOPICAL ANTIBIOTICS:

The application of local antibiotic drug delivery into the periodontal pocket or deep periodontal tissues signifies a higher or more effective drug concentration at the suspected site than those available with systemic antimicrobial therapy. Topical antimicrobial therapies are specifically recommended for residual pockets or at site where mechanical debridement becomes difficult to control the regrowth of a microbiota noxious to periodontal health. Numerous studies have shown that topical antibiotic can accomplish 50-100times greater therapeutic doses in sub-gingival sites than possible by systemic therapy [21].

A) Atridox:

Atridox is a biodegradable doxycycline polymer-liquid delivery system that hardens in the periodontal pocket to produce controlled release of an integrated drug. The liquid delivery system contains 10% antimicrobial agent doxycycline hyclate within a syringe that has a blunt-ended 23 gauge cannula resembling a periodontal probe. The tip of the cannula is introduced to the active infection or specified periodontal pocket site followed by release of doxycycline

hyclateuntil it fills the entire depth of pocket. Within 1 to 2 minutes the drug begins to harden inside the pocket on contact with the fluid/moisture surface which is further packed into the pocket using the blunt side of the moistened curette or any blunt-ended instrument [22].

B)Arestin:

Arestin is a recently approved (Food and Drug administration (FDA)) local antibiotic delivery system for sub-gingival placement. 2% concentration of minocycline is encapsulated into biodegradable microsphere in a gel carrier alongside with microsphere containing minocycline hydrochloride (11mg) that adheres to deep periodontal pocket or active target sites allowing a controlled constant release. Studies have shown 2-syringe mixing system for the controlled release of doxycycline resulted in significant reduction in colonization of P. gingivalis [23].

C) Actisite:

Actisite is a tetracycline hydrochloride antibiotic fiber-delivery system that contains polymer, 25% ethylene vinyl acetate saturated with tetracycline Hcl (12.7mg). The flexible fibres are folded and packet into a periodontal pocket that releases tetracycline at a constant rate over a period of 14 days. It is recommended in patients with >5mm periodontal pocket depth that bleeds and those who had not responded to mechanical non-surgical debridement/therapy [24].

D) Elyzol:

Elyzol(25%) is a metronidazole benzoate 40% gel suspended in a mixture of glycerol mono-oleate, when comes in interaction with the gingival crevicular fluid showed a minimum inhibitory concentration (MIC) of 14ug/ml. Studies have shown even after one application over a period of 24 hours the metronidazole concentration still remain above minimal inhibitory concentration for 50% destruction of significant periodontal pathogens [25].

VI.CONCLUSION

A successful antimicrobial therapy is influenced by the host-immune response, patient's periodontal status and microbial ecology of the oro-pharyngeal cavity and various local and systemically associated risk factors. Almost, all the previous available literature studies have shown that the risk of using antimicrobials such as adverse drug reaction, systemic side effects, increase antimicrobial resistance and intolerability ultimately resulted in restricted periodontal application in uncertain patients or conditions. One should always remember that antibiotics should be used only as a conjunction with mechanical debridement, based on understanding the biofilm characteristics rather than primary treatment option since an inappropriate use will ultimately result in resistance and ineffectiveness. Thus proper, optimal, effective and cautious use of systemic or local antibiotics is highly critical in the treatment of periodontal diseases.

Acknowledgement:None

Conflict of interest: Nil

REFERENCES

1) López R, Fernández O, Baelum V. Social gradients in periodontal diseases among adolescents. Community Dent Oral Epidemiol 2006; 34: 184-96.
2) Kinane DF. Periodontitis modified by systemic factors. Ann Periodontol 1999; 4: 54-63.
3) Slots J, Chen C. The oral microflora and human periodontal disease. In: Tannock GW, ed. Medical Importance of the Normal Microflora. London: Kluwer Academic Publishers, 1999: 101–127.
4) Slots J. Selection of antimicrobial agents in periodontal therapy. Journal of periodontal research. 2002 Oct;37(5):389-98.
5) Aurer A, PlanEak D. Antimicrobial treatment of periodontal diseases. ActaStomat Croat. 2004 Mar 15;38:67-72.
6) Paddmanabhan P. Antimicrobials in treatment of periodontal disease-A review. IOSR J Dent Med Sci. 2013;4:19-23.
7) Barca E, Cifcibasi E, Cintan S. Adjunctive use of antibiotics in periodontal therapy. Journal of Istanbul University Faculty of Dentistry. 2015;49(3):55.
8) Herrera D, Alonso B, León R, Roldán S, Sanz M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. Journal of clinical periodontology. 2008 Sep;35:45-66.
9) Hokari T, Morozumi T, Komatsu Y, Shimizu T, Yoshino T, Tanaka M, Tanaka Y, Nohno K, Kubota T, Yoshie H. Effects of antimicrobial photodynamic therapy and local administration of minocycline on clinical, microbiological, and inflammatory markers of periodontal pockets: a pilot study. International journal of dentistry. 2018 Apr 5;2018.
10) Manas D, Srinivas SR, Jithendra KD. Role of antibiotics in periodontal therapy. Bangladesh Journal of Medical Science. 2009;8(4):91-101.
11) Magnusson I, Lindhe J, Yoneyama T, Liljenberg B: Recolonization of a subgingivalmicrobiota following scaling in deep pockets. J ClinPeriodontol 1984; 11:193– 207.
12) Vyas D, Deshpande NC, Dave D. Effect of systemic doxycycline on scaling and root planing in chronic periodontitis. J Integr Health Sci 2019;7:8-12.
13) Loesche WJ. Rationale for the use of antimicrobial agents in periodontal disease. International journal of technology assessment in health care. 1990 Apr;6(3):403-17.
14) Guerrini L, Monaco A, Pietropaoli D, Ortu E, Giannoni M, Marci MC. Antibiotics in dentistry: a narrative review of literature and guidelines considering antibiotic resistance. The Open Dentistry Journal. 2019 Nov 15;13(1).

15) Collins JG, Offenbacher S, Arnold RR. Effects of a combination therapy to eliminate Porphyromonasgingivalis in refractory periodontitis. Journal of periodontology. 1993 Oct;64(10):998-1007.
16) Tenenbaum H, Jehl F, Gallion C, Dahan M. Amoxicillin and clavulanic acid concentrations in gingival crevicular fluid. Journal of clinical periodontology. 1997 Nov;24(11):804-7.
17) Winkel EG, Van Winkelhoff AJ, Barendregt DS, Van der Weijden GA, Timmerman MF, Van der Velden U. Clinical and microbiological effects of initial periodontal therapy in conjunction with amoxicillin and clavulanic acid in patients with adult periodontitis: A randomised double-blind, placebo-controlled study. Journal of clinical periodontology. 1999 Jul;26(7):461-8.
18) Jiao Y, Tay FR, Niu LN, Chen JH. Advancing antimicrobial strategies for managing oral biofilm infections. International journal of oral science. 2019 Oct 1;11(3):1-1.
19) Kumar SS, Mittal M, Khanna P. Role of antibiotics in the treatment of periodontal disease-an overview. Internet J Microbiol. 2012.
20) Schmidt EF, Bretz WA. Benefits of Additional Courses of Systemic Azithromycin in Periodontal Disease: CASE REPORT. New York State Dental Journal. 2007 Jun 1;73(4):40.
21) Mombelli A, Schmid B, Rutar A, Lang NP: Persistence patterns of Porphyromonasgingivalis, Prevotellaintermedia/nigrescens, and Actinobacillusactinomycetemcomitans after mechanical therapy of periodontal disease. J Periodontol 2000;71:14– 21.
22) Javali MA, Vandana KL. A comparative evaluation of atrigel delivery system (10% doxycycline hyclate) Atridox with scaling and root planing and combination therapy in treatment of periodontitis: A clinical study. Journal of Indian Society of Periodontology. 2012 Jan;16(1):43.
23) Lessem J, Hanlon A. A post-marketing study of 2805 patients treated for periodontal disease with Arestin. Journal of the International Academy of Periodontology. 2004 Oct 1;6(4 Suppl):150-3.
24) Kinane DF. Local antimicrobial therapies in periodontal disease. Annals of the Royal Australasian College of Dental Surgeons. 2000 Oct;15:57.
25) Stoltze K. Elimination of Elyzol® 25% Dentalgel matrix from periodontal pockets. Journal of clinical periodontology. 1995 Mar;22(3):185-7.