Power System Technology
ISSN:1000-3673

Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

Antibiotics in Periodontics: Past, Present, and Future Perspectives

1Majid noor aldeen alyamani, 2Suaad Hassan Alzahrani, 3Raniah Abdullatif Faden, 4Heba Khalid. Alshalawi, 5Afnan Hashem Mohsen Balkhy, 6Hesham Abdullah Alowaimer, 7Rami Mohammed Al-selami, 8Abdulmonem Abdulaziz Al-hawaidi, 9Dr.Salah Nasser Alokaili

1General dentist, Mushrifah Primary Health Care Centre, Jeddah 2nd Cluster, Ministry of Health, Jeddah, Saudi Arabia

2General Nursing, Mushrifah primary Health Care Center,Jeddah 2nd Cluster, Ministry of Health, Jeddah , Saudi Arabia

3General Dentistry, East Riyadh Dental Centre, Riyadh 2nd Cluster, Ministry of Health, Riyadh, SAU

4General dentistry, king salman hospital , Riyadh 1st Cluster, Ministry of Health , Riyadh.

5General Dentist, Al Takhasosi primary Health Care Center, Makkah Helth care Cluster, Ministry of Health, Makkah, Saudi Arabia

6Maxillofacial Specialist, Buraidah Central Hospital, AlQassim Health Cluster, Ministry of Health, Imtithal Jaffer Alsaihati,Dental Hygienist,Ministry of Health,Riyadh,Saudi Arabia

7General Dentistry, Alwaha Primary Health Care East Jeddah Hospital, Jeddah 1st cluster, Ministry of Health Jeddah .saudi arabia

8General Dentistry, East Riyadh Dental Centre, Riyadh 2nd cluster , Ministry of Health, Riyadh, Saudi Arabia

9Consultant of Periodontics and Implant Dentistry, Riyadh Dental Hospital, King Saud Medical City, Riyadh first health cluster, ministry of health , Saudi Arabia.

Introduction

Periodontitis, a multifaceted disease, is a chronic biofilm-induced inflammatory condition which leads to the destruction of the periodontal apparatus [1-3]. “Scaling and root planning” constitutes the bulk of the periodontal therapeutic intervention but this mechanical periodontal treatment alone may not always be beneficial alone in complex and difficult anatomical situations such as deep pockets and furcation defects [4-6]. So, along with mechanical debridement, treatment regimens employing antibiotics and antiseptics, as well as antibacterial agents, are more effective than mechanical debridement alone. Antibiotics can be given locally or systemically. Numerous investigations have suggested that periodontitis patients can benefit from receiving systemic antibiotics [7-10]. Systemic antibiotics, such as

Power System Technology
ISSN:1000-3673

Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

amoxicillin (with or without clavulanic acid) [11-13], azithromycin [14, 15] clindamycin [16], doxycycline [17], metronidazole [12, 16], tetracycline [17], and certain combinations of these are some of the therapy options [17, 19, 20]. However, there is a complete paradigm shift in the modern era regarding this concept.

Forms of antibiotic usage

Antibiotics usage in periodontal treatment can be seen in:

• Systemic administration

• Local drug delivery

• Host modulation.

Systemic administration

Rationale of systemic antibiotic therapy: A successful periodontal treatment is mostly carried out by a thorough mechanical debridement, but despite that some patients experience progressive clinical attachment loss because of the periodontal pathogens that can evade the host immune system. The red complex bacteria get attached to the soft tissue wall of the periodontal pocket making the supportive maintenance therapy phase difficult for the patient [21].

Also, periodontal infections like periodontal abscess, acute necrotizing gingivitis, etc. necessitates antibiotics prescription. Aggressive form of periodontitis, refractory periodontitis demands antibiotic therapy. Systemically compromised patients need to be administered with antibiotics along with mechanical therapy for better clinical results [22].

Selection of antibiotic:

The factors governing the decision for selection of antibiotics are:[23]

1. Age of patient: It may affect pharmacokinetics of many antibiotics e.g. tetracyclines accumulate in the developing teeth and bones.

2. Renal and hepatic function: Drug modification becomes necessary in case of impaired kidney/ liver function.

3. Local factors: The conditions such as the presence of pus and secretions, necrotic material and foreign body, low pH etc prevailing at the site of infection greatly affect the action of antibiotics.

4. Drug allergy: History of previous exposure to an antibiotic and any allergic reaction should be obtained.

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

5. Impaired host defense: In an individual with normal host defense, a bacteriostatic antibiotic may be enough, while intensive therapy with bactericidal drugs are imperative in those with impaired host defenses.

6. Pregnancy: All antibiotics should be avoided in the pregnant females because of risk to the developing foetus.

7. Organism related considerations: Though the therapy is empirical most of the times, the likelihood of the most probable pathogen must be considered.

8. Drug factors: This includes the specific properties of antibiotics like spectrum of activity

Determinants of antibiotics administration and dosage:

Two critical factors should be specifically considered in selecting a systemic antibiotic in periodontal therapy:[24]

Gingival fluid concentration and Minimum inhibitory concentration (MIC).

1.The gingival fluid concentration (CGCF) provides information on the peak levels achieved by systemic delivery at the primary ecological niche for periodontal pathogens, the periodontal pocket.

2. The 90% minimum inhibitory concentration (MIC90) is an in vitro determination of the

concentration that will inhibit growth of 90% of the bacterial strains of a species that are tested. Antimicrobial activity can be defined as a relationship between CGCF and MIC90.

Principles of antibiotic dosing: [25]

1. Employ high doses for a short duration
2. Use an oral antibiotic loading dose
3. Achieve blood levels of the antibiotic at 2-8 times the minimal inhibitory concentration
4. Use frequent dosing intervals
5. Determine the duration of therapy by the remission of disease

Commonly used antibiotics

Extensively used antibiotics in periodontics fall under the following broad category:

• Tetracycline

• Metronidazole

• Penicillin

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

• Cephalosporin

• Clindamycin

• Ciprofloxacin

• Macrolide

•Aminoglycosides.

Tetracycline

Pharmacology

1. It is produced naturally from certain species of Streptomyces or derived semi-synthetically.

2. Bacteriostatic drugs, effective against rapidly multiplying bacteria and gram-positive bacteria than gram negative bacteria.

3. Concentration in the gingival crevice is 2-10 times that in serum.[26]

4. Possess unique non-antibacterial characteristics such as collagenase inhibition,[27] inhibition of neutrophil chemotaxis, anti-inflammatory effects,[24] inhibition of microbial attachment [28] and root surface conditioning.[29]

Mode of action

Act by inhibition of protein synthesis by binding to 30 S ribosomes in the susceptible organism.[23]

Dosage regimen- 250 mg four times daily

Minocycline

1. Effective against a broad spectrum of microorganisms. It also suppresses spirochetes and motile rods

2. Although associated with less phototoxicity and renal toxicity than tetracycline, it may cause reversible vertigo.

3. Also, it has good periodontal effect as it yields gingival fluid levels 5 times that of blood levels.[30]

Doxycycline

1. Same spectrum of activity as minocycline.

2. Dosage: given as once daily and absorption from gastrointestinal tract which is only slightly altered by calcium, metal ions, or antacids.[26] The recommended dosage is 100

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

mg bid the first day, then 100 mg o.d. To reduce gastrointestinal effects, 50 mg can be taken as bid.

Metronidazole

Pharmacology

1. A synthetic nitroimidazole compound with bactericidal effects primarily exerted on obligate gram-positive and gram-negative anaerobes.

2. The concentrations of the drug measured in gingival fluid are generally, slightly less than that in plasma.

Mode of action: Metronidazole acts by inhibiting DNA synthesis.

Penicillin

Pharmacology

1. Natural and semi synthetic derivatives of broth cultures of the penicillium mould.

2. Narrow spectrum and bactericidal in nature. Major activity in the gram-positive spectrum. Only the extended spectrum penicillin, such as ampicillin and amoxicillin, possess substantial antibacterial antimicrobial activity for gram-negative species.[24]

Mode of action: Interfere with the synthesis of bacterial cell wall, inhibit the transpeptidases so that cross linking does not take place.

Cephalosporins

Pharmacology

1. Used for infections that might otherwise be treated with penicillin.

2. Resistant to several beta-lactamases normally active against penicillin.

Mode of action: Same mode of action as penicillin, i.e., inhibition of bacterial cell wall synthesis. However, they bind to different proteins than those which bind penicillin.[30]

Clindamycin

Pharmacology

Effective against anaerobic bacteria, and in patients allergic to penicillin.

Mode of action: Inhibition of protein synthesis by binding to 50 S ribosome.

Ciprofloxacin

Pharmacology

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

1. A fluorinated 4-quinolone antibiotic available for oral administration.
2. A potent inhibitor of gram-negative bacteria (all facultative and some anaerobic putative periodontal pathogens), including Pseudomonas aeruginosa
3. MIC90 values ranging from 0.2 to 2 microg/ml. [24]

Mode of action: Inhibition of bacterial DNA replication and transcription by inhibiting the enzyme DNA gyrase, an enzyme unique to prokaryotic cells. [23]

Macrolides

Pharmacology

1. Contain a poly-lactone ring to which one or more deoxy sugars are attached.
2. It can act both as a bacteriostatic or bactericidal drug, depending on the concentration of the drug and the nature of the microorganism.
3. The macrolide antibiotics used for periodontal treatment include erythromycin, spiramycin, and azithromycin.

Mode of action**:** Inhibits protein synthesis by binding to the 50 S ribosomal subunits and it also interferes with translation.

Azithromycin

Clinical use

1. Effective against anaerobes and gram-negative bacilli.
2. It has been proposed that azithromycin penetrates fibroblasts and phagocytes in concentrations 100-200 times greater than that of extracellular Compartment.[26]
3. Dosage: Single dose of 250 mg/day for 5 days after an initial loading dose of 500 mg.

Aminoglycosides

1. Inhibit protein synthesis by binding irreversible to a particular protein or proteins of the 30 S ribosomal subunit.

CLINICAL USE OF THESE DRUGS IN PERIODONTICS

1. TETRACYCLINE

- Adjuncts in the treatment of localized aggressive periodontitis (LAP).
- It arrests bone loss and suppresses A. actinomycetemcomitans levels in conjunction with scaling and root planning.

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

2. METRONIDAZOLE

- For treating gingivitis, acute necrotizing ulcerative gingivitis, chronic periodontitis, and aggressive periodontitis.
- Metronidazole as a sole therapy is inferior, so, it should be used in combination with other antibiotics. The most commonly prescribed regimen is 250 mg tid for 7 days.

3. PENCILLIN

- In the management of patients with aggressive periodontitis, in both localized and generalized forms.
- Exhibits high antimicrobial activity at levels that occur in GCF for most of the periodontal pathogens

4. CLINDAMYCIN

Clindamycin assisted in stabilizing refractory patients. Dosage was 150 mg qid for 10 days.[31]

5. CIPROFLOXACIN

- Facilitates the establishment of a microflora associated with periodontal health, minimal effects on streptococcus species, which are associated with periodontal health.
- At present, ciprofloxacin is the only antibiotic in periodontal therapy to which all strains of *A. actinomycetemcomitans* are susceptible.

In periodontics SEQUENTIAL SYSTEMIC ANTIBIOTICS and COMBINATION THERAPY is used.

- SEQUENTIAL SYSTEMIC ANTIBIOTICS: Antibiotics that are bacteriostatic (e.g., tetracycline) generally require rapidly dividing microorganisms to be effective. They do not function well if a bactericidal antibiotic (e.g., amoxicillin or metronidazole) is given concurrently. When both types of drug are required, they are best given serially, not in combination, to avoid unfavourable interaction yet derive the benefit of both.[26]
- COMBINATION THERAPY : A combination of metronidazole and amoxicillin (MA) has shown to be an effective antibiotic regime to combat Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis-associated periodontal infections.[32]
- Metronidazole ciprofloxacin combination is effective against A. actinomycetemcomitans. Metronidazole targets obligate anaerobes, and ciprofloxacin targets facultative anaerobes. This is a powerful combination against mixed infections. Studies of this drug combination in the treatment of refractory periodontitis have documented marked clinical improvement.[33]

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

Local drug delivery (LDD)

Systemic antibiotic coverage comes with adverse reactions. Based on the nature of the periodontal destruction and the condition of the patient, alternative mode of antibiotic administration like local drug delivery can be opted.

For localized adjunctive pharmacological periodontal therapy, there are three main approaches:

1. subgingival irrigation,
2. mouth rinse (toothpaste or varnish),
3. periodontal administration of local delivery antimicrobial agents.

Types Of Locally Delivered Antibiotics

1. Metronidazole
2. Tetracycline
3. Minocycline
4. Doxycycline

CLINICAL INDICATIONS

1. Furcation Involvement
2. Residual pockets
3. Smokers
4. Patients with diabetes and periodontitis

Local drug delivery systems (LDDS)

LDDSs manage the release of locally administrated drugs that are indicated as an adjunct to periodontal treatment. There are two groups: LDDSs loaded with therapeutical agents used as an adjunct in non-surgical periodontal therapy, and LDDSs loaded with drugs used as an adjunct in surgical periodontal therapy.[34]

1. Fibers:

Fibers are a reservoir-type delivery system loaded with the selected therapeutic agent,
agent, placed circumferentially into the periodontal pocket by an applicator and main-
placed circumferentially into the periodontal pocket by an applicator and maintained in situ by a cyanoacrylate adhesive or a periodontal dressing [35-37].

In 1979, Goodson et al. [38],introduced hollow fibers impregnated with tetracyclines which allowed the introduction of less than 1/1000 of the normal amount of tetracyclines by systemic administration.

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

Other anti-microbial molecules, including metronidazole or azithromycin, are efficient too, giving better results than mechanical debridement alone in periodontal treatment [39-40].

2. Strips and Films:

Strips and films (SFs) are thin matrix bands in which drugs are dissolved throughoutthe polymer.

The first materials proposed in the fabrication of strips and films were acrylics loaded with different kind of antibiotics [41]. As they were non-biodegradable, they were associatd with a second intervention for the removal [42].

To overcome such a disadvantage, new bioabsorbable materials were introduced, including poly-hydroxybutyric acid and poly lactic-co-glycolic acid (PLGA), atelocollagen, gelatin, chitosan/PLGA, and more [43].

Non-biodegradable SFs released the therapeutical agent by diffusion. Meanwhile, biodegradable SF released by diffusion and erosion [44].

3. Microparticles:

Microparticles are solid spherical polymer structures with a diameter from 1 to 1000 µm, loaded with a drug that spreads uniformly throughout the polymer matrix. They are very easy to administer and provide a prolonged release of the drug but are not readily retained in the target sites.They are delivered via various carrier systems such as chips, dental pastes/gel systems, and direct injection into the pocket [35]. Drugs such as minocycline and metronidazole are used in the way.

4. Nanosystems

Nanosystems are characterized to have very small sizes that allow them to be suitable for the areas where other forms of LDDSs do not arrive, such as the pocket area below the gum line. They are directly injected in the pocket area or placed via other carrier systems (ex. gels) [35]. They include micellas, metallic and polymeric nanoparticles, liposomes, and nanofibers. Polymeric nanoparticles loaded with minocycline by emulsification–diffusion have shown good results, having 96% of the minocycline released after 12 days and very good clinical outcomes in terms of periodontal healing [45]. Chitosan, which is a natural material, characterized by high biodegradability, nontoxicity, and antimicrobial properties [46], has been largely used in the fabrication of nanoparticles. PLGA loaded with doxycycline (DOX) has shown a sustained release after administration in periodontal pockets [47].

5. Gels

Gels are very popular in dentistry, thanks to their multiple advantages: they have high biocompatibility and bioadhesivity, very easy administration, and easy fabrication. They are placed by wide-port needle syringes in the periodontal site [35]

Power System Technology
ISSN:1000-3673

Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

Advantages of local drug delivery systems (LDDS)[38,48-50]

- High bioavailability of the drug;
- controlled drug release;
- bypass of the hepatic metabolism;
- no gastrointestinal issues;
- reduction in frequent doses;
- mini-invasiveness of some LDDSs;
- high compliance of the patient;
- use of drugs that are not compatible with systemic administration (ex. Chlorhexidine);
- no interaction with other drugs.

Disadvantages of local drug delivery systems (LDDS) [38,48-50]

- Difficulty of management of some types of LDDS,
- some of them have difficulty to provide sufficient drug-concentration;
- the need of reintervention for the oldest LDDS;
- the need of further investigations to assess which kind of LDDS is the best one;
- high costs.

Host modulation therapy (HMT)

Host modulation therapy is the treatment concept which reduces destruction and stabilizes or even regenerates inflammatory tissue by modifying host response factors [51]. This concept focuses on two different categories of treatment modalities. They are either by the

inhibition of the host inflammatory responses [52] or by the resolution [53].

Non-antibiotic tetracyclines are widely used and they act by their pleiotropic mechanism of action [54]. They have extracellular mechanisms, intracellular mechanism and proanabolic effects. They are as follows [55]:

a. Extracellular mechanisms of non-antibiotic tetracycline:

a. Inhibition of the activated matrix metalloproteinases in the connective tissue by binding of Zn++ and Ca++ binding sites.
b. Inhibition of the activation of proactive matrix metalloproteinases by the reactive oxygen species independent of cation binding.
c. Inactivation of the proactive matrix metalloproteinases by the partial proteolysis.
d. Indirect inhibition of serine proteinases.

b. Cellular mechanisms by decreased expression of proactive matrix metalloproteinases by decreasing inflammatory cytokines, phospholipases A2 and nitric oxide.

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

c. Proanabolic effect is by up regulation of collagen synthesis and osteoblastic activity and increased bone formation.

Potential Targets of Host Modulation Therapy: [56]

• Matrix metalloproteinases: eg. TIMPs, Tetracylines

• Arachidonic acid metabolites: eg. NSAIDs

• Bone metabolism:eg. Bisphosphonates

• Pro-inflammatory Cytokines: eg. blockade of receptors for IL-1, TNF

• Other inflammatory mediators such as Nitric oxide (NOS) syntase activity (eg. mercapto ethyl guanidine),Nuclear factor kappa β, Endothelial cell adhesion molecules, Disruption of cell signaling pathways such as RANK /RANKL /osteoprotegerin axis.

Modulation of Host Matrix Metalloproteinases

Inhibitors of MMPs are either

A. **Endogenous eg.** α2 macroglobulin, Tissue inhibitors of MMP (TIMP)

B. **Exogenous (synthetic)** eg. Tetracycline, CMT, SDD, others (Batimastat (BB-94) and marimastat (BB-2516) are synthetic, low-molecular weight MMP inhibitors).

Sub antimicrobial Dose Doxycycline (SDD)

SDD is approved by the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency. It was introduced under the trade name Periostat (CollaGenex Pharmaceuticals Inc., Newtown, PA). It is a 20-mg dose of doxycycline hyclate that is taken twice daily for periods of 3–9 months. The rationale for using SDD as a host response modulator is that it inhibits the activity of MMPs by a variety of synergistic mechanisms independent of any antibiotic properties like:

• Direct inhibition of active MMPs by cation chelation (dependent on Ca2+- and Zn2+-binding properties)

• Inhibits oxidative activation of latent MMPs (independent of cation-binding properties)

• Downregulates expression of key inflammatory cytokines (interleukin-1, interleukin-6 and tumor necrosis factor-α) and prostaglandin E2

• Scavenges and inhibits production of reactive oxygen species produced by Neutrophils

• Inhibits MMPs and reactive oxygen species thereby protecting a1-proteinase inhibitor

• Stimulates fibroblast collagen production

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

• Reduces osteoclast activity and bone resorption

• Inhibits osteoclast MMPs[57]

Chemically modified tetracycline's (CMTs)

In 1987, Golub et al [58] described a new use for the first CMT (4-dedimethylamino tetracycline or CMT-1), which is devoid of antibacterial activity due to the removal of the

dimethylamino group from the carbon-4 position of the "A" ring of the drug molecule, but which retains its anticollagenase activity.

A series of 10 different chemically modified tetracyclines have since been identified, called chemically modified tetracycline's 1-10, nine of which were found to retain their anticollagenase but to have lost their antimicrobial properties.

Other host modulatory agents [59]

1. Modulation of Arachidonic Acid Metabolites
a. Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)
b. Triclosan
c. Omega3 fatty acid
2. Anticytokine Drugs
a. Infliximab (Remicade)
b. Etanercept (Enbrel)
c. Anakinra (Kineret)
3. Regulation of Bone Remodeling
a. Macrophage colony stimulating factor (M-CSF)
b. Receptor Activator of Nuclear Factor kappa B Ligand (RANKL)

Locally Administerd Host Modulating Agents [59]

1. Enamel Matrix Proteins
2. Bone morphogenetic proteins (BMPs)
3. Bisphosphonate

CONCLUSION

Although non-surgical therapy is the keystone in the periodontal treatment. It not only helps in attaining clinical attachment gain and periodontal pocket reduction but also helps in the eradication of the periodontal pathogens. However, treating periodontitis in medically compromised and other forms as aggressive periodontitis is made possible with a predictable success rate by the adjunctive antibiotic therapy as scaling and root planning alone is not sufficient in such cases. Antibiotics both systemically and locally help in attaining an ideal result from periodontal therapy. Host modulation helps in management of the pro-

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

inflammatory cytokines, Reactive Oxygen species (ROS), Reactive Nitrogen Species (RNS) and other inflammatory components. Thus overall a judicial usage of antibiotics on ethical background along with mechanical therapy will warrant a success.

REFERENCES

1. Hajishengallis G. Immunomicrobial pathogenesis of periodontitis: Keystones, pathobionts, and host response. Trends Immunol 2014; 35(1): 3-11.

2. Bartold PM, Van Dyke TE. Periodontitis: A host-mediated disruption of microbial homeostasis. Unlearning learned concepts. Periodontol 2000 2013; 62(1): 203-17.

3. Loos BG, Van Dyke TE. The role of inflammation and genetics in periodontal disease. Periodontol 2000 2020; 83(1): 26-39.

4. Doungudomdacha S, Rawlinson A, Walsh TF, Douglas CWI. Effect of non-surgical periodontal treatment on clinical parameters and the numbers of *Porphyromonas gingivalis, Prevotella intermedia* and *Actinobacillus actin omycetemcomitans* at adult periodontitis sites. J Clin Periodontol 2001; 28(5): 437-45.

5. Caffesse RG, Sweeney PL, Smith BA. Scaling and root planing with and without periodontal flap surgery. J Clin Periodontol 1986; 13(3): 205-10.

6. Loos B, Claffey N, Egelberg J. Clinical and microbiological effects of root debridement in periodontal furcation pockets. J Clin Periodontol 1988; 15(7): 453-63.

7. Keestra JAJ, Grosjean I, Coucke W, Quirynen M, Teughels W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: A systematic review and meta-analysis. J Periodontal Res 2015; 50(3): 294-314.

8. Herrera D, Sanz M, Jepsen S, Needleman I, Roldán S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planing in periodontitis patients. J Clin Periodontol 2002; 29(Suppl. 3): 136-59.

9. Haffajee AD, Socransky SS, Gunsolley JC. Systemic anti-infective periodontal therapy. A systematic review. Ann Periodontol 2003; 8(1): 115-81.

10. Feres M, Figueiredo LC, Soares GMS, Faveri M. Systemic antibiotics in the treatment of periodontitis. Periodontol 2000 2015; 67(1): 131-86.

11. Kim S-J. The effectiveness of subgingival scaling and root planing in calculus removal. J Korean Acad Periodontol 1998; 28(2): 371.

12. Feres M, Haffajee AD, Allard K, Som S, Socransky SS. Change in subgingival microbial profiles in adult periodontitis subjects receiving either systemically-administered amoxicillin or metronidazole. J Clin Periodontol 2001; 28(7): 597-609.

Power System Technology
ISSN:1000-3673

Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

13. Rodrigues DC, Taba M Jr, Novaes AB Jr, Souza SLS, Grisi MFM. Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. J Periodontol 2003; 74(9): 1361-7.
14. Dastoor S F, Travan S, Neiva R F, Rayburn L A, Giannobile W V, Wang H-L. Effect of adjunctive systemic azithromycin with periodontal surgery in the treatment of chronic periodontitis in smokers: A pilot study. J Periodontol 78(10): 1887-96.
15. Haas AN, de Castro GD, Moreno T, *et al.* Azithromycin as an adjunctive treatment of aggressive periodontitis: 12-months randomized clinical trial. J Clin Periodontol2008; 35(8): 696-704.
16. Sigusch B, Beier M, Klinger G, Pfister W, Glockmann E. A 2-step non-surgical procedure and systemic antibiotics in the treatment of rapidly progressive periodontitis. J Periodontol 2001; 72(3): 275-83.
17. Sibaja ME. A pilot study. Prof Dev EMI Fac Mex 2020; 18–20: 18-20.
18. Lindhe J, Liljenberg B, Adielsson B. Effect of long-term tetracycline therapy on human periodontal disease. J Clin Periodontol 1983; 10(6): 590-601.
19. Rooney J, Wade WG, Sprague SV, Newcombe RG, Addy M. Adjunctive effects to non-surgical periodontal therapy of systemic metronidazole and amoxycillin alone and combined. J Clin Periodontol 2002; 29(4): 342-50.
20. Guerrero A, Griffiths GS, Nibali L, *et al.* Adjunctive benefits of systemic amoxicillin and metronidazole in non-surgical treatment of generalized aggressive periodontitis: A randomized placebo-controlled clinical trial. J Clin Periodontol 2005; 32(10): 1096-107.
21. Slots J; Research, Science and Therapy Committee. Systemic antibiotics in periodontics. J Periodontol. 2004 Nov;75(11):1553-65. doi: 10.1902/jop.2004.75.11.1553. PMID: 15633334.
22. Kapoor A, Malhotra R, Grover V, Grover D. Systemic antibiotic therapy in periodontics. Dent Res J (Isfahan). 2012 Sep;9(5):505-15. doi: 10.4103/1735-3327.104866. PMID: 23559912; PMCID: PMC3612184.
23. Tripathi KD. Antimicrobial drugs: General considerations. In: Tripathi KD, editors. Essentials of medical pharmacology. 5th ed. New Delhi: Jaypee Publishers; 2003. p. 627-40.
24. Goodson JM. Antimicrobial strategies for treatment of periodontal diseases. Periodontol 2000 1994;5:142-68.
25. Pallasch TJ. Pharmacokinetic principles of antimicrobial therapy. Periodontol 2000 1996;10:5-11.

Power System Technology
ISSN:1000-3673

Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

26. Jolkovsky DL, Ciancio S. Chemotherapeutic agents. In: Carranza FA, Newman MG, Takei HH, Klokkevold PR, editors. Clinical periodontology. 10th ed. Philadelphia: WB Sa unders; 2006. p. 798-812.

27. Golub LM, Ramamurthy N, McNamara TF, Gomes B, Wolff M, Casino A, et al. Tetracyclines inhibit tissue collagenase activity. Anew mechanism in the treatment of periodontal disease. J Period ontal Res 1984;19:651-5.

28. Lantz MS, Ray T, Krishanasami S, Perrson DE. Subinhibitory concentrations of tetracycline alter fibrinogen binding by Bucferoidesinterrnedius. Antimicrob Agents Chemother 1987;31:1915-8.

29. Wikesjö UM, Baker PJ, Christersson LA, Genco RJ, Lyall RM, Hic S, et al. A biochemical approach to periodontal regeneration: Tetracycline treatment conditions dentin surfaces. J Peri odont Res 1986;21:322-9.

30. Walker CB. Selected antimicrobial agents: Mechanisms of action, side effects and drug interactions.Periodontol 2000 1996;10:12-28.

31. Walker CB, Gordon JM, Magnusson I, Clark WB. A role for antibiotics in the treatment of refractory periodontitis. J Per iodontol 1993;64:772-81.

32. van Winkelhoff AJ, Winkel EG. Antibiotics in periodontics:Right or wrong? J Periodontol 2009;80:1555-8.

33. Rams TE, Feik D, Slots J. Ciprofl oxacin/metronidazole treatment of recurrent adult periodontitis. J Den t Res 1992;71:319.

34. Amato M, Santonocito S, Polizzi A, Tartaglia GM, Ronsivalle V, Viglianisi G, Grippaudo C, Isola G. Local Delivery and Controlled Release Drugs Systems: A New Approach for the Clinical Treatment of Periodontitis Therapy. Pharmaceutics. 2023 Apr 21;15(4):1312. doi: 10.3390/pharmaceutics15041312. PMID: 37111796; PMCID: PMC10143241.

35. Rajeshwari, H.R.; Dhamecha, D.; Jagwani, S.; Rao, M.; Jadhav, K.; Shaikh, S.; Puzhankara, L.; Jalalpure, S. Local drug delivery systems in the management of periodontitis: A scientific review. J. Control. Release 2019, 307, 393–409.

36. el Kenawy, R.; Bowlin, G.L.; Mansfield, K.; Layman, J.; Simpson, D.G.; Sanders, E.H.; Wnek, G.E. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend. J. Control. Release 2002, 81, 57–64.

37. Chou, S.F.; Carson, D.; Woodrow, K.A. Current strategies for sustaining drug release from electrospun nanofibers. J. Control.Release 2015, 220, 584–591.

Power System Technology
ISSN:1000-3673
Received: 16-10-2024 Revised: 05-11-2024 Accepted: 02-12-2024

38. Goodson, J.M.; Haffajee, A.; Socransky, S.S. Periodontal therapy by local delivery of tetracycline. J. Clin. Periodontol. 1979, 6, 83–92.

39. Reise, M.; Wyrwa, R.; Müller, U.; Zylinski, M.; Völpel, A.; Schnabelrauch, M.; Berg, A.; Jandt, K.D.; Watts, D.C.; Sigusch, B.W.Release of metronidazole from electrospun poly(L-lactide-co-D/L-lactide) fibers for local periodontitis treatment. Dent. Mater. 2012, 28, 179–188.

40. Zhang, Z.; Zheng, Y.; Bian, X. Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: A meta-analysis of randomized controlled clinical trials. J. Periodontal. Res. 2016, 51, 275–283.

41. Deasy, P.B.; Collins, A.E.; MacCarthy, D.J.; Russell, R.J. Use of strips containing tetracycline hydrochloride or metronidazole for the treatment of advanced periodontal disease. J. Pharm. Pharmacol. 1989, 41, 694–699.

42. Larsen, T. In vitro release of doxycycline from bioabsorbable materials and acrylic strips. J. Periodontol. 1990, 61, 30–34.

43. Wei, Y.; Deng, Y.; Ma, S.; Ran, M.; Jia, Y.; Meng, J.; Han, F.; Gou, J.; Yin, T.; He, H.; et al. Local drug delivery systems as therapeutic strategies against periodontitis: A systematic review. J. Control. Release 2021, 333, 269–282.

44. Pillai, O.; Panchagnula, R. Polymers in drug delivery. Curr. Opin. Chem. Biol. 2001, 5, 447–451.

45. Yao, W.; Xu, P.; Pang, Z.; Zhao, J.; Chai, Z.; Li, X.; Li, H.; Jiang, M.; Cheng, H.; Zhang, B.; et al. Local delivery of minocycline-loaded PEG-PLA nanoparticles for the enhanced treatment of periodontitis in dogs. Int. J. Nanomed. 2014, 9, 3963–3970.

46. Kaya, M.; Baran, T.; Erdo˘gan, S.; Mente¸s, A.; Özüsa˘glam, M.A.; Çakmak, Y.S. Physicochemical comparison of chitin and chitosan obtained from larvae and adult Colorado potato beetle (Leptinotarsa decemlineata). Mater. Sci. Eng. C Mater. Biol. Appl. 2014, 45, 72–81.

47. Moura, L.A.; Ribeiro, F.V.; Aiello, T.B.; Duek, E.A.; Sallum, E.A.; Nociti Junior, F.H.; Casati, M.Z.; Sallum, A.W. Characterization of the release profile of doxycycline by PLGA microspheres adjunct to non-surgical periodontal therapy. J. Biomater. Sci. Polym. Ed. 2015, 26, 573–584.

48. Wei, Y.; Deng, Y.; Ma, S.; Ran, M.; Jia, Y.; Meng, J.; Han, F.; Gou, J.; Yin, T.; He, H.; et al. Local drug delivery systems as therapeutic strategies against periodontitis: A systematic review. J. Control. Release 2021, 333, 269–282.

Power System Technology
ISSN:1000-3673

Received: 16-10-2024 **Revised: 05-11-2024** **Accepted: 02-12-2024**

49. Rajeshwari, H.R.; Dhamecha, D.; Jagwani, S.; Rao, M.; Jadhav, K.; Shaikh, S.; Puzhankara, L.; Jalalpure, S. Local drug delivery systems in the management of periodontitis: A scientific review. J. Control. Release 2019, 307, 393–409.

50. Kornman, K.S. Controlled-release local delivery antimicrobials in periodontics: Prospects for the future. J. Periodontol. 1993, 64,782–791.

51. Shinwari MS, Tanwir F, Hyder PR, Bin Saeed MH. Host modulation therapeutics in periodontics: role as an adjunctive periodontal therapy. J Coll Physicians Surg Pak. 2014 Sep;24(9):676-84. PMID: 25233975.

52. Williams RC, Jeffcoat MK, Howell TH, Rolla A, Stubbs D, Teoh KW, Reddy MS, Goldhaber P. Altering the progression of human alveolar bone loss with the non-steroidal anti-inflammatory drug flurbiprofen. J Periodontol. 1989 Sep;60(9):485-90. doi: 10.1902/jop.1989.60.9.485. PMID: 2677301.

53. Van Dyke TE. Pro-resolving mediators in the regulation of periodontal disease. Mol Aspects Med. 2017 Dec;58:21-36. doi: 10.1016/j.mam.2017.04.006. Epub 2017 May 18. PMID: 28483532; PMCID: PMC5660638.

54. Golub LM, Lee HM, Ryan ME, Giannobile WV, Payne J, Sorsa T. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. Adv Dent Res. 1998 Nov;12(2):12-26. doi: 10.1177/08959374980120010501. PMID: 9972117.

55. Golub LM, Lee HM. Periodontal therapeutics: Current host-modulation agents and future directions. Periodontol 2000. 2020 Feb;82(1):186-204. doi: 10.1111/prd.12315. PMID: 31850625; PMCID: PMC6973248.

56. Offenbacher S. Periodontal diseases: pathogenesis. Ann Periodontol 1996;1:821- 78

57. Kornman KS. Host Modulation as a Therapeutic strategy in the Treatment of Periodontal disease. Clin Infect Dis 1999;28:520-6

58. Preshaw PM. Host response modulation in Periodontics.Periodontol 2000 2008;48:92-110.

59. Bhoir, Vrushali. (2020). Host modulation therapy: A review. International Journal of Dental Science and Innovative Research. 3. 207-223.