

Probiotics and Antibiotics in Periodontal Therapy- A Review

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Abstract: Periodontal disease is a biofilm associated polymicrobial disease that involves a complex interplay between the pathogenic bacteria and the host. The biofilm nature of the disease limits any long-term success in the treatment of this disease, as sooner or later, the biofilm is re-established. Over the years, a number of treatments have been used as adjuncts to scaling and root planing to maximize benefits of periodontal therapy. Probiotics have been used for a number of years in the field of general medicine for the treatment of inflammatory bowel disease, prevention of allergies, etc., Microbial plaque is the primary etiology for periodontal diseases and its removal with mechanical therapy is considered as gold standard to achieve periodontal health .in addition to that, many chemotherapeutic agent including antimicrobial host modulation agents have been used to achieve better results.

Key Words: synbiotics, probiotics, antibiotics, pathobiotechnology, bion.

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I. An Introduction To Probiotics And Antibiotics:

The probiotic term was derived from Greek word, meaning “for life”[4],it may also be defined as live microorganisms which,when administered in adequate amounts confer health benefits on the host (FAO/WHO report-2001). Most commonly used in probiotic preparation are lactobacillus ,bifidobacterium, eschcheria,enterococcus,bacillus,and streptococcus .along with bacterial species,some fungal strains belonging to saccharomyces have also been used in probiotic preparation.

An antibiotic is a naturally occurring, semisynthetic, or synthetic type of anti-infective agent that destroys or inhibits the growth of selective microorganisms, generally at low concentration.Anti-infective agents can be administered locally or orally .when administered orally, many of these agents can be found in gingival crevicular fluid (GCF).with either purpose is to reduce the number of bacteria present in the diseased periodontal pocket.

HISTORICAL ASPECT:

FOR PROBIOTICS:

- In modern times, the history of the use of probiotics goes back to 1908 when a biologist and Nobel laureate elie Metchnikoff described the beneficial effect of the use of lactobacillus from yogurt.
- The term ‘probiotic’ was coined in 1965 by Stillwell and Lilly. The term ‘prebiotic was coined by Gibson et al.in 1995.prebiotics are the nutrients that feed the probiotic bacteria.
- The term synbiotic is used when a product contains both probiotics and prebiotics. When both are combined, the survival of the bacteria in the intestine is enhanced.

FOR ANTIBIOTICS:

May be divided into 3 phases:

- The period of empirical use :Of moldy curd by Chinese on boils, chaulmoogra oil by Hindus in leprosy etc.,
- Ehrlich’s phase of dyes and organo metallic compounds (1890-1935) with the discovery of microbes in the later half on the 19th century and that they are the cause of many diseases: ehrlich toyed with the idea that if certain dyes could selectively stain microbes, they could also be selectively toxic to these organisms. Etc., he coined the term ‘chemotherapy’ because he used drugs of known chemical agents.
- The modern era of chemotherapy was ushered by Domagk in 1935 by demonstrating the therapeutic effect of prontosil sulfonamide dye, in pyogenic infection. But the later this was not essential. The phenomenon of antibiosis was demonstrated by Pasteur in 1877.

PROBIOTIC STRAINS IN ORAL CAVITY:

Culture based studies suggest that bifidobacterial are among the first anaerobes in the oral cavity Various bacterial species listed in the following table-1.

An essential property of a microorganism to be “an oral probiotic” is its ability to adhere and to and colonize surfaces in the mouth. Out of all bacterial species so far detected in the oral cavity ,lactobacilli genera constitute approximately 1% cultivable oral microflora. Using a polymerase chain reaction (PCR),

COMMERCIAL ORAL PREPARATIONS AVAILABLE:

Gum perio balance, Periobiotic, Bifidumbacterin, Acilact, ProDentis

COMMONLY USED ANTIBACTERIALAGENTS IN PERIODONTICS :

Beta-lactam antibiotic,Tetracyclines,Metronidazole,Macrolides, Aminoglycosides ,Fluoroquinolones, Vancomycin.

PROPERTIES OF PROBIOTICS AND ANTIBIOTICS

- It should be a strain, which is capable of exerting a beneficial effect on the host animal.it should enhance host immunity against pathogens.
- It should be non-virulent and non-pathogenic
- Preferred to be present as viable cells in large numbers.
- It should be capable of surviving and metabolizing in the gut environment(endurance to low Ph and carbon based acids)and should be able to maintain.
- genetic stability in oral microflora
- It should be able to influence the local metabolic activity.
- It should be stable and ,on storage, large numbers of viable bacteria must be able to survive.

ANTIBIOTICS:

- Should be specific for periodontal pathogens.
- Allogenic.
- Nontoxic.
- Substantive.
- Not in general use for treatment of other disease
- Inexpensive

RATIONALE FOR USING PRO AND ANTIBIOTIC AGENTS IN PERIODONTAL DISEASES:

- Eliminate ,reduce or alter the effects of microorganisms in the oral cavity and elevated levels of proinflammatory mediators.
- To reduce the tissue invading bacteria.[7]
- The various virulence factors secreted by various bacterial species have been shown to cause direct or indirect bone loss. Thus elimination or reduction of microbial load is essential to achieve periodontal health.
- Poor host defense.

MECHANISM OF ACTION:

FOR PROBIOTICS:

(1) Direct actions :

- Lactobacilli maintains the micro ecological balance in the oral cavity
- They have a direct interaction in dental plaque formation
- They compete with other organism for attachment of the tooth surfaces
- They produce chemicals that inhibit periodontal pathogens

(2) Indirect actions:

- They modulate systemic immune response in favors of the host
- They affect local immune response also
- They produce antioxidantsor act as antioxidants
- They reduce pathogen induced pro inflammatory cytokine production
- They prevent plaque formation by neutralizing free electrons
- They upregulate intestinal barrier integrity and mucin production.

FOR ANTIBIOTICS:

- Inhibit cell wall synthesis
- Causes leakage from cell membrane
- Inhibit protein synthesis
- Cause misreading of mRNA code and affect permeability
- Inhibit DNA gyrase
- Interfere with DNA function
- Interfere with DNA synthesis

MODE OF ADMINISTRATION:

✓ Systemic or local administration.

FOR PROBIOTICS: by lozenges, straw and tablets, milk, cheese, yogurt, mouth wash.

FOR ANTIBIOTICS: Tablets, capsules, ointments, mouthwash, gel, toothpaste.

CRITERIA FOR PRESCRIBING ANTIBIOTIC THERAPY:

- Whom to treat? The clinical condition of the patient should dictate the need for antibiotic therapy.
- Microbial culturing and culture sensitivity: should be selected on the basis of culturing of the plaque sample obtained from periodontal pocket and its culture sensitivity test.
- Starting the antibiotic therapy: the physical disruption of biofilm is essential to achieve maximum benefit from antibiotic therapy because bacteria in a well-organized biofilm are 500-1000 times more resistant to antibiotics as compared to planktonic bacteria.
- Consultation with the patient: the patient should be explained in detail the need for antibiotic therapy and its potential benefits.
- Choice of antibacterial systemic agents for administration: depends on the microbial analysis and antibiotic sensitivity test.
- Various factors which should be considered while choosing an antibiotic : choosing antibacterial agents for empirical therapy.
- Spectrum of chosen drug .
- Age of the patient
- Status of renal and hepatic function
- Patients with compromised host response
- Pregnancy
- Patient already taking medications.
- Drug allergy.

PRINCIPLES OF ANTIBIOTIC DRUG DOSING:

Based on minimum inhibitory concentration (MIC) and gingival fluid concentration (C_{gcf}). MIC₉₀ or minimum inhibitory concentration 90% is the concentration of drug that will inhibit the growth of 90% of bacterial strains of species that are tested in vitro.

The effectiveness of the drug in periodontal pocket is determined by the relationship between C_{gcf} and MIC₉₀.

DECISION MAKING IN DOSAGE:

FOR PROBIOTICS:

1. the most important concerned factor is the availability of the probiotic bacteria in the oral cavity. Generally, probiotics are delivered in dairy products (mainly fermented milk), as food supplements limited. Tablet forms or soft drinks. However, with these vehicles the oral availability of probiotics is limited
- 2) A better option is the administration of probiotics via lozenge form or chewing gum.

FOR ANTIBIOTICS:

- 1) Some antibacterial agents require a high concentration of the drug (above MIC) in plasma and tissues for effective bacterial killing. ex., metronidazole. On the other hand, other agents require a prolonged exposure to the bacteria to be effective. Ex-beta lactams.
- 2) The dosing interval depends on the plasma half-life of the drug.
- 3) The loading dose is necessary to quickly achieve the required plasma levels of the drug because after oral administration, it takes 6-12 hours to achieve required plasma and tissue levels of the drug.
- 4) The dose of the drug should achieve 2-8 times the minimal inhibitory concentration of the drug in plasma. This is because tissue barriers may impede the drug penetration into tissues.

5) The duration of the therapy should be continued until the infection is significantly resolved. It should allow the host defense system to overcome the infection. Most periodontal infections can probably be treated in 14 days or less duration of the antibiotic therapy.

LIMITATIONS IN USAGE OF PROBIOTIC AND ANTIBIOTIC THERAPY IN PERIODONTAL DISEASES:

FOR PROBIOTICS:

- a) Lactobacillus preparations are contraindicated in persons with a hypersensitivity to lactose or milk.
- b) *S. boulardii* is contraindicated in patients with yeast allergy.
- c) Used with caution in patients with immunosuppression, prematurity infants.
- d) Minor risks associated include the presence of a central venous catheter, diarrheal illness, cardiac valvular disease, concurrent administration with antibiotics.

FOR ANTIBIOTICS:

- a) Periodontal diseases are multifactorial disease. Bacterial etiology is the primary etiology of most periodontal diseases, but many systemic, environmental and genetic factors are also associated with periodontal disease progression.
- b) Multiple microorganisms are associated with periodontal diseases consisting of both gram positive and gram negative bacteria.
- c) The diagnosis is primarily made on the basis of clinical findings and not on the basis of microbiological analysis.

PROBIOTICS IN PERIODONTAL THERAPY:

PROBIOTICS IN HALITOSIS MANAGEMENT:

Volatile Sulphur compounds (VSC) are responsible for halitosis. Bacteria responsible for VSC production are *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Treponema denticola*. A probiotic strain (*Weissella cibaria*) possesses the ability to inhibit VSC production under both in vitro and in vivo conditions. It possesses great potential as a novel probiotic for use in the periodontium. Co-aggregation of *Fusobacterium nucleatum* with other periodontal pathogens results in secondary colonization of biofilm and contributes substantially to VSC production in the oral cavity.

Streptococcus salivarius produces bacteriocins, which inhibit bacteria producing VSC. Recently, a study showed that lozenges and gum containing *Streptococcus salivarius* decrease VSC in halitosis patients.

Probiotics are supplied along with prebiotic in the form of powder, sachet, gelatin capsules, or suspension. "BION" commercially available in Indian market (combination of pre- and probiotic) has 0.48 billion spores of *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Streptococcus Thermophilus*, and 0.10 billion spores of *Saccharomyces boulardii* along with 300 mg of fructo-oligosaccharides, is prescribed as single dose daily before meals in the morning.

Another important concern is the dose of probiotics required for adequate action; various studies have reported different values, 1×10^8 - 10^{10} , 1×10^9 - 10^{10} , 1×10^{10} - 10^{11} .

Some cases of bacteraemia and fungemia have been reported in immunocompromised individuals in gut syndrome and chronic diseases.[8] *Lactobacillus endocarditis* have been reported after dental treatment in a patient taking *Lactobacillus rhamnosus*. Reported cases of infection are extremely rare accounting to 0.05–0.4% of infective endocarditis and bacteraemia.

Futuristic approach in Probiotics :

The term "Patho-Biotechnology" was introduced by Sletor and Hill. It comprises of three basic approaches [1]

- a) Use of attenuated bacterial pathogens as vaccines
- b) Isolation and purification of pathogen specific immunogenic protein for direct application
- c) Equipping probiotics bacteria with genetic elements necessary to overcome stress outside host, inside host and antagonize invading pathogens.

Third approach is what is termed "designer probiotics". This approach employs probiotics to be engineered to express receptor mimic structures on their surface; few studies done are limited to gut, periodontal studies are lacking, but poses a great potential in this field to develop. Designer probiotics have been employed in treatment of HIV, also employed as a novel vaccine delivery vehicle.

In the future, various techniques such as molecular biology, nano-technology, and tissue engineering sciences, biochemical, microbiological and immunological techniques are expected to come together in bringing up an ideal or near ideal probiotic preparation specifically for the treatment of periodontitis.

ANTIBIOTICS IN PERIODONTAL THERAPY:

Tetracycline, Metronidazole and beta lactams are the most widely used agents for treating periodontal conditions.

As pointed by van Winkel Hoff et al a sufficiently high dosage of metronidazole or other antibiotics must be prescribed to ensure efficacy in periodontal treatment [13]

Tenebaum et al. showed that effective levels of amoxicillin and clavulanic acid in the gingival crevicular fluid well above the minimal inhibitory concentrations of some periodontopathic bacteria could be achieved after multiple drug applications.

A peak plasma concentration of 2- 2.5 mg/ ml occurs 2-4 hours following oral administration of repeated dose of tetracycline Tetracycline are bacteriostatic can suppress *A. actinomycetemcomitans* appears to concentrate in periodontal pockets, have been shown to suppress collagenase activity in crevicular fluid .

Literature states that factors which influence antibiotic therapy include substantivity of a drug which is seen in tetracycline and its derivatives minocycline, oxytetracycline, chlortetracycline strongly adsorb to tooth surface retaining their antimicrobial activity.

Antibiotic regimens in periodontal therapy can be mono or combination antibiotic therapy. Tetracycline- hcl, minocycline, doxycycline which inhibit collagenolytic activity , metronidazole which specifically target anaerobic microorganisms, clindamycin which actively act against gram -ve anaerobes, having main association with periodontal flora, azithromycin a macrolide antibiotic has broad spectrum activity and prolonged drug concentration in tissues and serum [13] , amoxicillin a semisynthetic penicillin excellent activity against gram positive and negative bacteria is absorbed well following oral administration and penetrates in GCF [13] are the following drugs recommended for treating periodontists

Preventing emergence of bacterial resistance, increased synergy and lowering dose of individual antibiotics, also broadening the antimicrobial range of therapeutic regimen beyond that attained by a single antibiotic are the advantages of combination therapy.

COMBINATION ANTIBIOTIC THERAPY:

Sequencing of antibiotic therapy overcomes potential risk of antagonism between bacteriostatic and bactericidal antibiotics [13] . To date, serial drug regimens studied in periodontics include systemic doxycycline administered initially, followed by either Augmentin or metronidazole [13] .

Combination therapy of metronidazole- amoxicillin resulted in less gingival bleeding and it is reported by lo-pezzard coworkers [13] . Also Winkel et al. demonstrated that combination of metronidazole – amoxicillin therapy reduced pocket depth significantly compared with control.

TOPICAL USE OF ANTIBIOTICS:

The adjunctive use of locally applied or systemic administration of antimicrobial and host response modulatory medications has been proposed. Localized therapy has received significant attention because of site specific pattern destruction of periodontal infection and the potential side effects of systemic antimicrobial agents are reduced. Tetracycline has been promoted in several systems (powder, gel, irrigation, fibers) [14] .

Tetracycline fibers are non-resorbable with 12.7mg of tetracycline hydrochloride powder function in a controlled delivery device above 1590ug/ml crevicular fluid for 10 days.

Studies shows that tetracycline derivatives doxycycline and minocycline which are more lipophilic than the parent compound resulted in better adsorption following systemic delivery and better penetration into the bacterial cell.

In a recent meta-analysis ,states that 2% minocycline gel improved reduction in periodontal probing depth and gain in attachment. Also a microsphere containing minocycline hydrochloride (11mg) adheres to periodontal pocket allowing a controlled sustained release [11]

Two syringe mixing system for the controlled release of doxycycline resulted in greater reduction of frequency of *P. gingivalis* [11]

A topical medication containing an oil-based metronidazole 25% dental gel(glycerol mono-oleate and sesame oil) has been tested in a number of studies.it is applied in viscous consistency to the pocket,where it is liquidized by the body heat and then hardens again,forming crystals in contact with water.

Two 25% gel applications at a 1 week interval have been used.

II. Conclusion

Probiotics are opposite to antibiotics thus are free from developing resistance, they are body's own resident flora hence are most easily adjusted to the host. Future perspectives is to achieve knowledge and evidence regarding recent advances of drug delivery, its efficacy in periodontium, effect on prognosis of periodontal disease after antibiotic administration in adjunct to mechanical therapy. Thus clinical, interventional and epidemiological studies are required with adequate sample size.

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(TABLE: 1)

Lactobacillus species	Bifidobacterium species	Streptococcus species	Saccharomyces species	Others
Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus lactis, Lactobacillus Helvetius, Lactobacillus salivarius, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus rhamnosus, Lactobacillus johnsonii, Lactobacillus reuteri, Lactobacillus fermentum, Lactobacillus delbrueckii	Bifidobacterium bifidum, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium breve, Bifidobacterium lactis, Bifidobacterium adolescentis	s.thermophilus s.salivarius subsp, thermophilus	s.boulardii	Bacillus cereus, Escherichia coli Enterococcus faecium, Enterococcus faecalis, Propionibacterium freudenre

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